Twenty-fourth Annual Meeting
San Francisco, June 18-22, 1958

VOLUME XXXIII NUMBER 1

DISEASES

of the

CHEST

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AMERICAN COLLEGE CHEST PHYSICIANS

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VOLUME XXXIII JANUARY, 1958 NUMBER 1

CONTENTS

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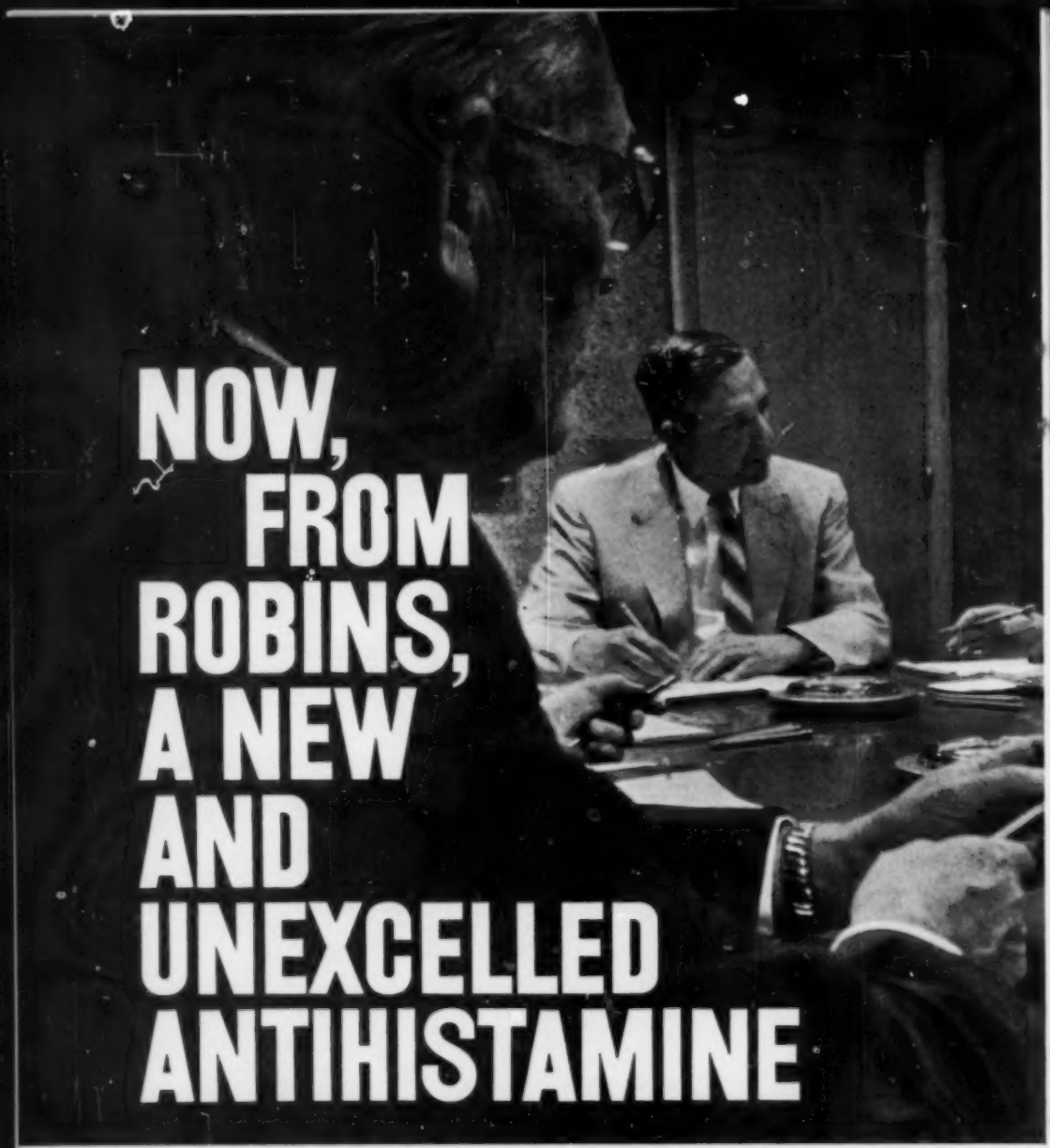

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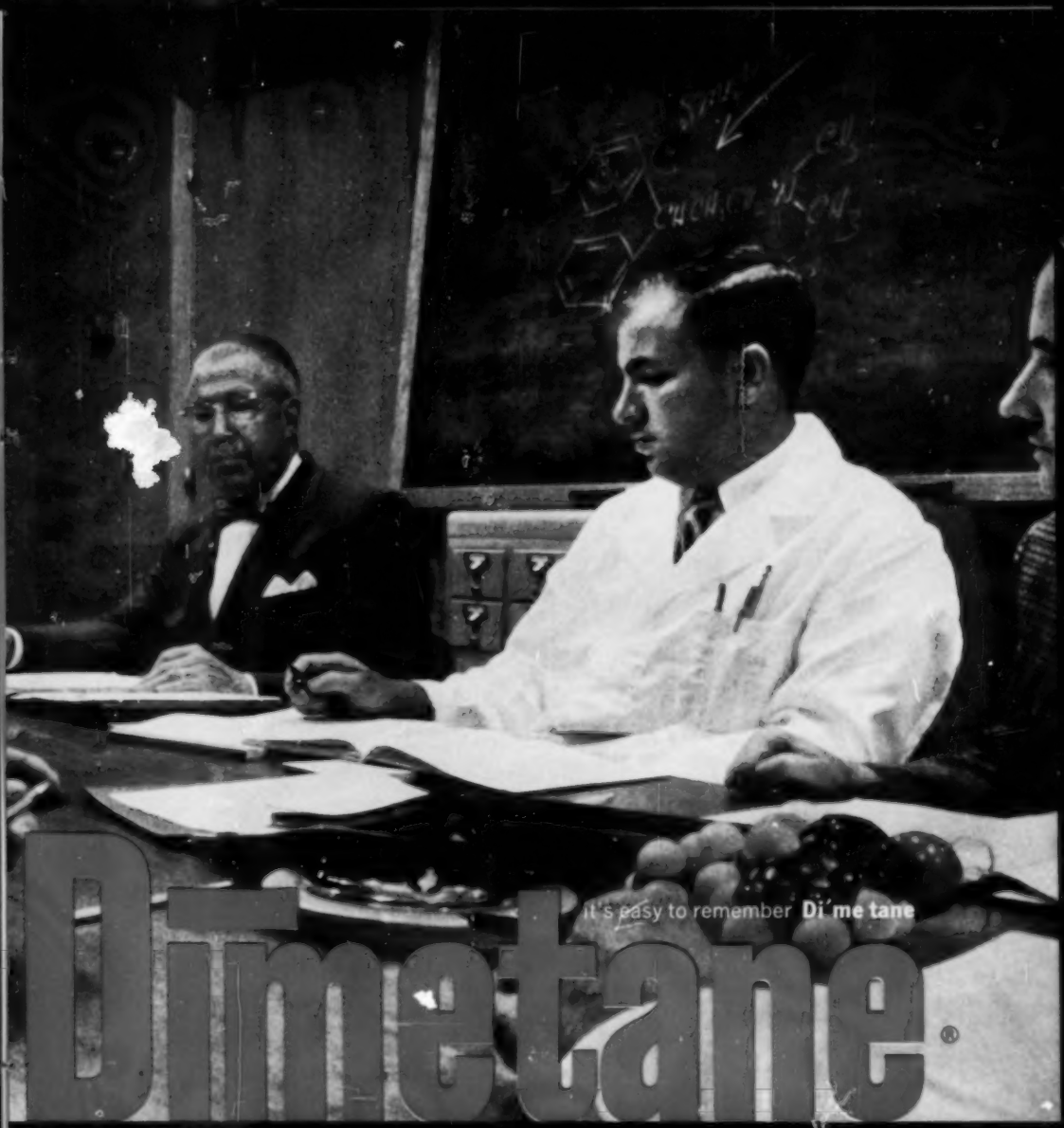

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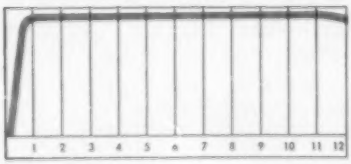

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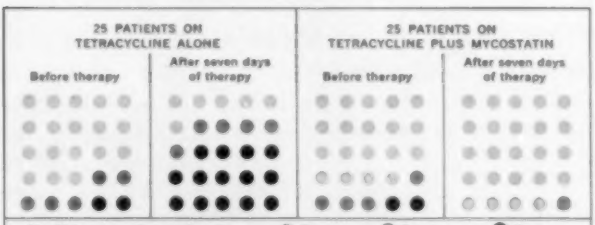

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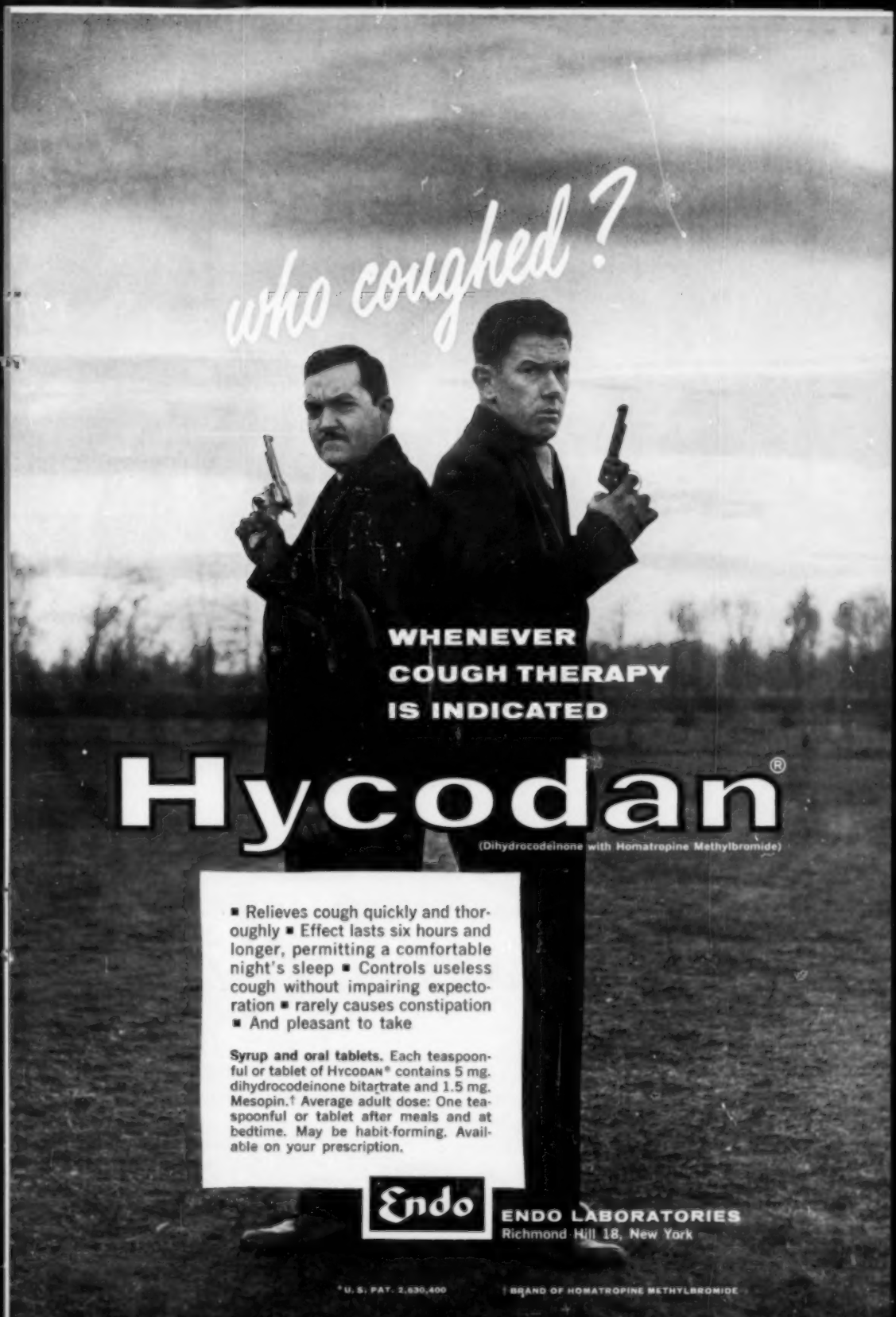
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(1) Feinberg, A. R., and Feinberg, S. M.: J.A.M.A. *160*:264, 1956. (2) Schwartz, E.: J. Allergy *26*:206, 1955. (3) Skaggs, J. T.; Bernstein, J., and Cooke, R. A.: J. Allergy *26*:201, 1955. (4) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Dis. Chest *27*:515, 1955.

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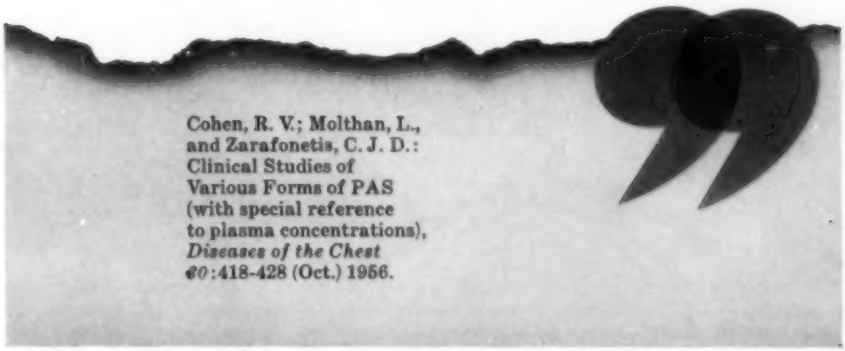

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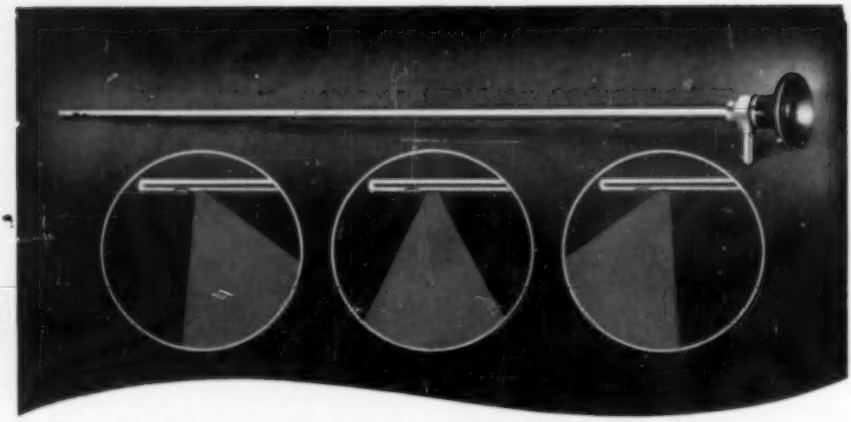

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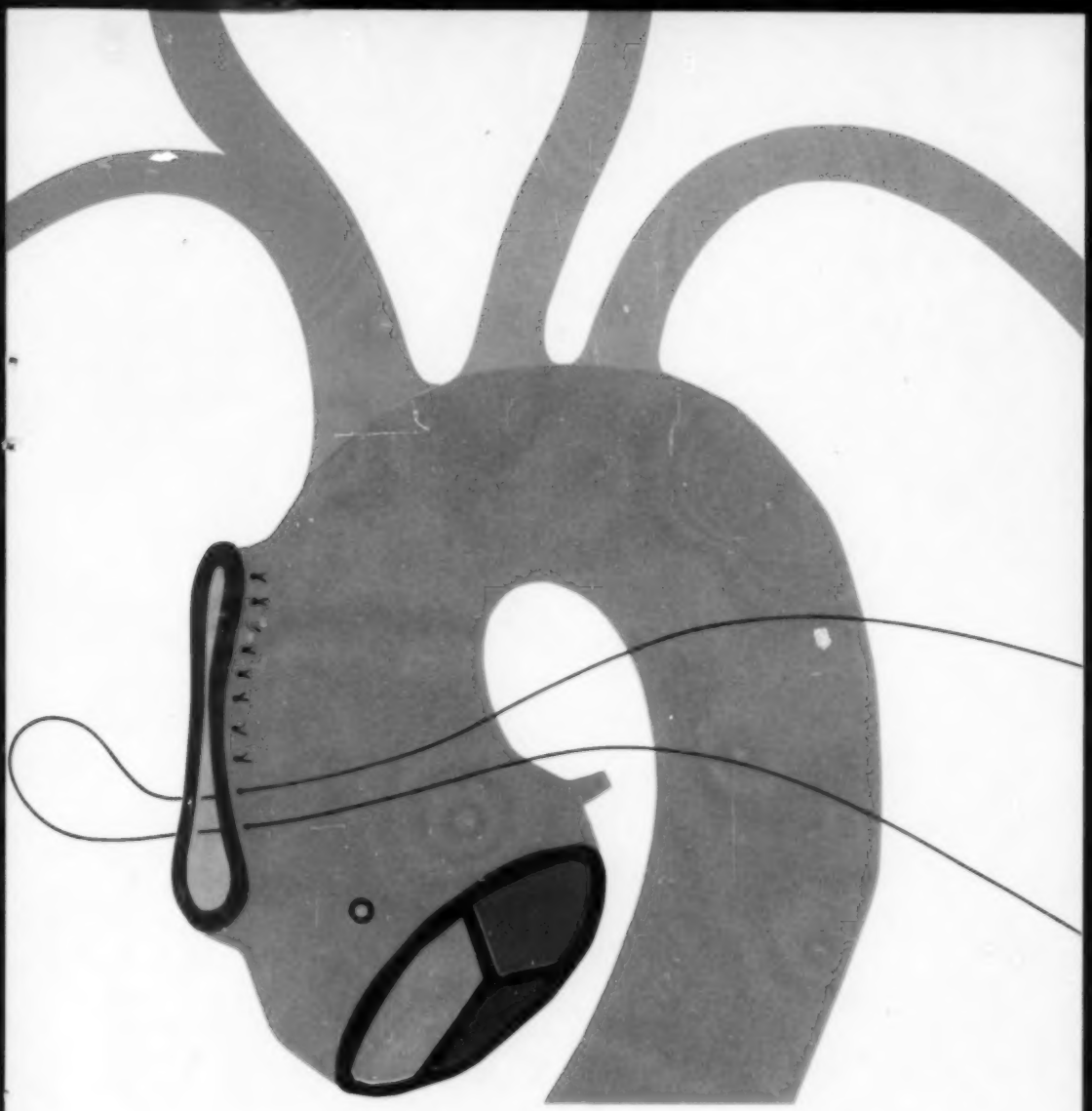

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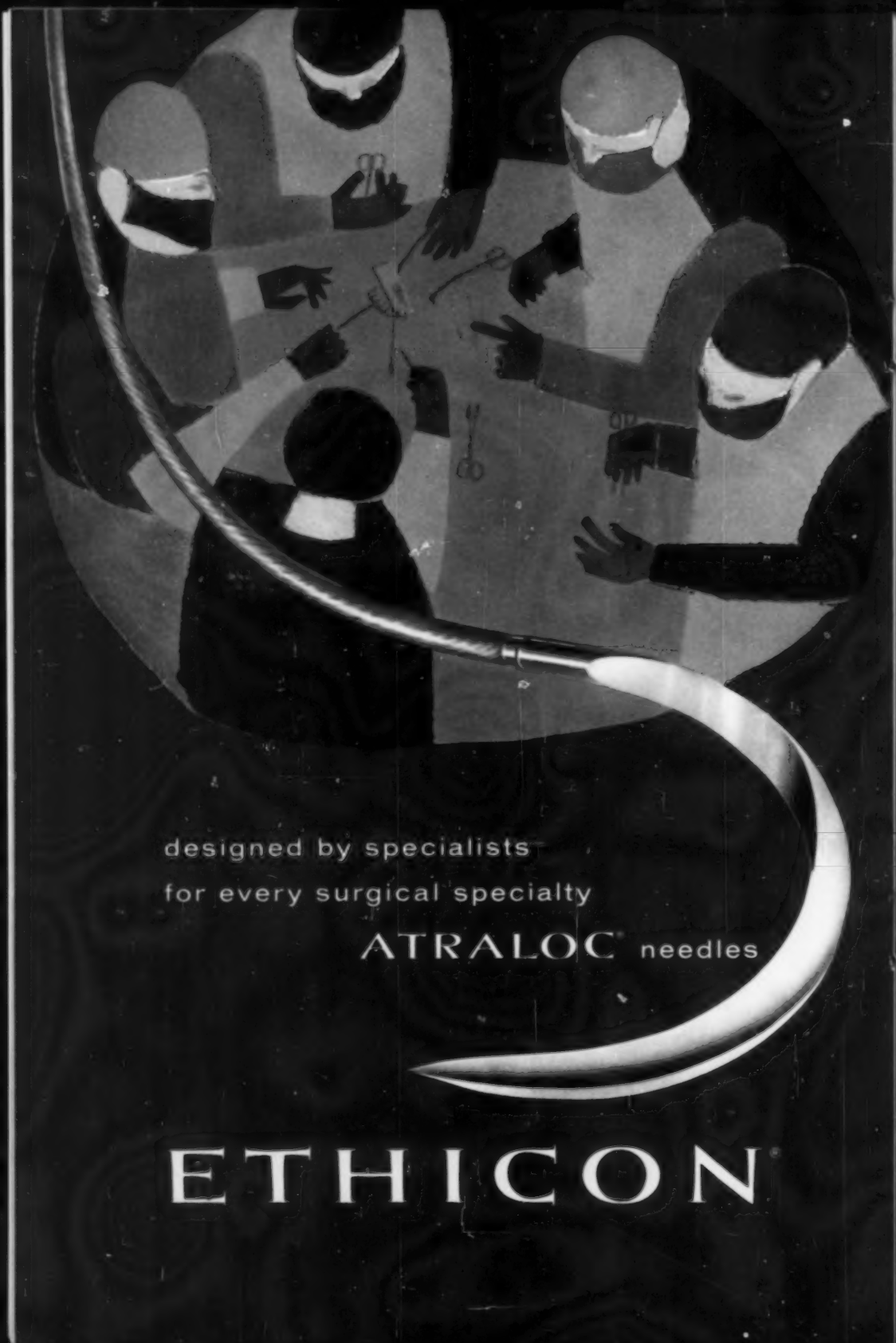
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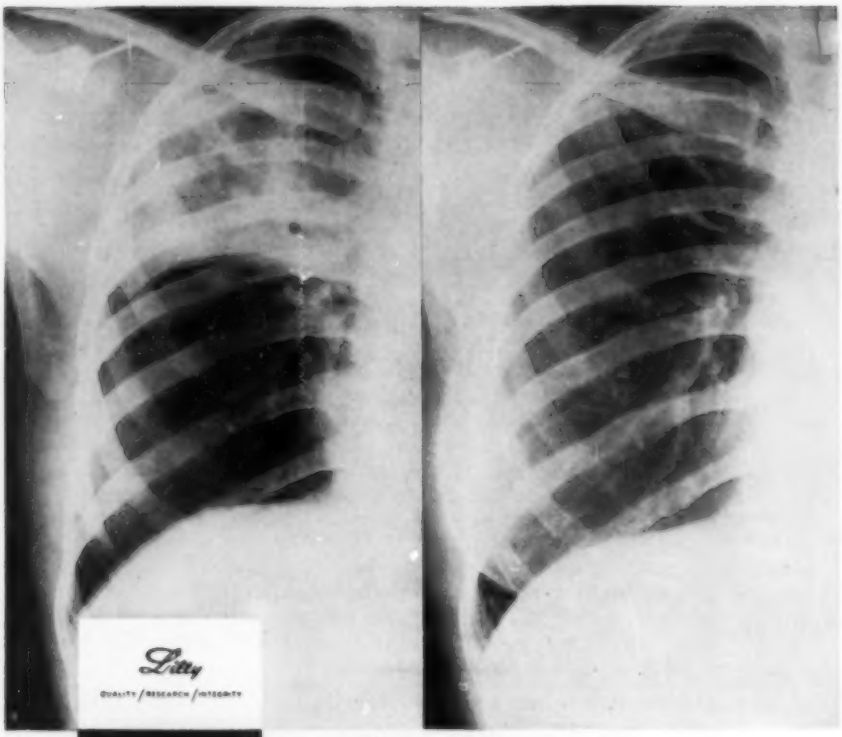

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DISEASES of the CHEST

VOLUME XXXIII JANUARY, 1958 NUMBER 1

Antituberculous Chemoprophylaxis with Isoniazid Preliminary Note

A. OMODEI ZORINI, M.D., F.C.C.P.*
Rome, Italy

During the past few years, attention has been paid by pediatricians to the striking therapeutic results obtained in miliary tuberculosis and in tuberculous meningitis by the administration of isoniazid, but in very large doses of 20-30 and even 40 mg./Kg. of body weight. INH, in these doses, being well tolerated by children, seems to have a real bacteriocidal action; from these observations, the idea arose of applying this therapeutic method in skin-positive subjects. Also, to sterilize the infected organism and to avoid clinical evolution of tuberculous disease in adulthood.

It seems that we have reached a decisive stage of the battle against tuberculosis, in that BCG vaccination in children might be replaced by a method of positive treatment in a prophylactic sense. Thus, INH, in large doses, could be administered in all primary tuberculous infections, even though the latter are not severe.

These observations stimulated me to attempt to resolve the problem quickly through the institution of a series of investigations having both experimental and clinical features. But before either the method of investigation or the results obtained are stated, one has to examine the respective experimental and theoretical bases with reference to comparable pathology which would justify a chemoprophylaxis approach with isoniazid in man.

Assuming that adequate treatment with INH in children could approach or equal the antituberculous vaccination with BCG, one has to demonstrate that:

1) the drug does not produce toxic effects even if administered in large doses and for a long period;
2) tuberculosis does not develop in subjects put in mass contamination during treatment with isoniazid, when the drug is administered in adequate doses at regular intervals.
3) tuberculosis is not present when treatment is stopped following an adequate therapeutic period;
4) treatment with isoniazid develops a maximal resistance to infection, whether endogenous or exogenous.

In our institute, during recent years, systematic and complete investigations have been carried out on isoniazid in guinea pig experimental tuberculosis, the results of which may furnish a partial answer to all the above mentioned conditions.

*Director, Carlo Forlanini Institute and Professor, Rome University.

Besta, Pana, Lucchesi and Valenti, in the course of extended investigations, showed that the action of INH in the dose of 10 mg./Kg. in experimental tuberculosis of guinea pigs, provoked by a strain of moderate virulence in the infecting dose 1/10 of mg. subcutaneously, is very effective, lasting and of a greater therapeutic effect than streptomycin, which, in similar conditions, allowed continued development of specific foci after treatment was suspended. This action of INH is particularly apparent in the lungs where the histologic findings, besides confirming the absence of specific lesions, shows the possibility of establishment in these organs of a process of specific fibrosis better with INH than with the other antituberculosis drugs. It is possible to consider this action causing fibrosis, already outlined in man, as the expression of greater possibilities of anatomic recovery of tuberculosis in those cases treated with chemoantibiotics.

S. H. Ferebee and C. E. Palmer at Chamblee, Georgia, recently performed an interesting and extensive experiment with the following conclusions: 1) moderate quantity of isoniazid (5 mg./Kg.) administered in the drinking water of animals, prevents a large endoperitoneal inoculum of virulent tubercle bacilli from killing the guinea pigs and also from influencing their growth; 2) the beneficial drug effects last for some time because deaths from tuberculosis were not registered in a period of 16 weeks, during which drug administration had been stopped, and the weight gain was similar to the controls; 3) primary tuberculous infection under protection of INH has been able to develop in animals a remarkable condition of resistance to a secondary virulent infection of the same dose of bacilli, given during the period of INH withdrawal. The degree of resistance acquired is comparable to that obtained by the BCG vaccination of guinea pigs.

Unfortunately, the results of the allergic tests, as well as of the anatomic-pathologic and bacteriologic examinations of these investigations, are not known to us, so that some reservations regarding the conclusions of the American authors are maintained.

In veterinary medicine, investigations are reported which are in agreement with those mentioned above.

B. Moretti and B. Pedini of Perugia University studied tuberculous cows for 60 days with special interest regarding eight calves of these cows. Four were treated with INH in a dosage of 10 mgr./Kg. daily intramuscularly and four were untreated. Necropsy examinations at the end of the study showed complete absence of tuberculous lesions in four treated calves, while in the controls, the presence of pathologic lesions of the lymph nodes and the pulmonary system, with characteristic exudative and caseous features, were detected.

L. Badiali, also of Perugia University, in a similar type of investigation, studied four calves kept in contact with infected animals. Two calves had been treated and two untreated. After an interval of 120 days, necropsy examinations were performed. Disseminated tuberculous lesions were noted involving bronchial and mediastinal nodes, lung, and the pleura of the untreated animals; no lesions were detected in the treated animals.

Emulsions of mediastinal, bronchial and mesenteric lymph nodes from the treated animals, inoculated in guinea pigs, did not produce tuberculous lesions.

These experiments demonstrate the effectiveness of antituberculous protection in the veterinary field, because INH can prevent the growth and the multiplication of tubercle bacilli.

Another problem intimately related to chemoprophylaxis with INH is the very much discussed and so far unresolved question of the decreased virulence of the eventual vaccinating power of INH resistant tuberculous strains.

Recently, Barnett, Bushby and Mitchison, Hobby, Lenert, and Auerbach, Hamilton and Nassau, carried out experimental investigations comparing the immunizing power of INH-resistant strains with that of BCG. They reached the conclusion that INH-resistant tubercle bacilli produces in guinea pigs immunizing properties against experimental tuberculosis and a degree of protection comparable to that obtained with BCG itself.

At the Forlanini Institute, C. Pana, M. Lucchesi, and G. Storniello have been conducting extensive investigations on the vaccinating power of INH-resistant strains and they have reached the conclusion that infection with these strains appears to be adequate in producing a relative immunity in laboratory animals, which, although not preventing the formation of new specific lesions by strains of moderate virulence, does suppress the pathologic reaction considerably with the possibility of a slowly progressive regression of the lesion.

I will end this brief bibliographic review by mentioning the small number of similar experiments of chemoprophylaxis going on in man, besides our own. In December, 1955, Professor Debre announced a work being carried out in Paris, Lyons, Bordeaux, Nancy, under the direction of Professor Bugnard, Dr. Schwartz, and Dr. Lotte, on 4000 skin-positive children, of whom 2000 are treated daily with INH in doses of 20 mg./Kg. for a period of six months and left in their households. The results of this experiment, so far, are unknown.

In Japan, recently, some experiments of chemoprophylaxis have been carried out, mainly with PAS, and at present an experiment is being carried out on 800 skin-positive subjects being treated with 5-8 gr. of PAS daily, combined in some cases with INH in the dose of 200 mgr. for two days a week (Chiba, Totsuka, Tojima). It is interesting to note that the incidence of tuberculosis in 90 subjects treated with PAS in the dose of 10 gr. daily for a period of 3 to 6 months in 1951 has been, so far, 2.2 per cent, while among controls in the same number and conditions of contagion, ten cases of tuberculosis (11.1 per cent) have developed.

On the basis of a recent communication from Dr. Lincoln, a statistical investigation has been started in the United States and Puerto Rico, in 31 pediatric clinics on a total number of 1100 skin-positive children, the majority with clinical symptoms of a primary node pulmonary tuberculosis.

At present, INH is administered in the dosage of 5 mgr./Kg. for one year to half of these, and to the other half an inactive substance is ad-

ministered. The investigation is under the patronage of the Federal Service of Public Hygiene and, so far, the results are unknown.

Personal Investigations

At the Forlanini Institute, since January 1956, we have been carrying out a wide series of investigations on INH in regard to its prophylactic value, attempting to demonstrate: 1) the good drug tolerance and its therapeutic effectiveness even if administered in large doses of 20 mg./Kg. daily for long periods; 2) the protective power of isoniazid in experimental animals against a virulent infection and its ability to provide an immunization against a new infection by virulent strains; 3) the practical possibility of experimental evaluation of antituberculous prophylaxis in skin-positive or skin-negative children particularly when living in infected households.

The first and second sequences of investigations have been finished already, while the third is going on and therefore we can give only some preliminary notice.

Up to 1952, and also in 1953, at the National Meeting of Phthisiology in Turin, we advocated therapy in large doses with INH, but the strongest supporters of large doses are mainly pediatricians.

At the meeting in Paris in December, 1955 at the "Centre International de l'Enfance," Debre, Raymond, and Naveau, de Castro Ferreira, reported on the excellent results obtained on this program; in Italy also, De Toni, Brusa, Caronia, are following a therapeutic scheme where INH is administered in doses of 10-13 mgr./Kg. daily.

In collaboration with L. Praloran, D. Oricchio, Bagnoli, and Banoli, we have been treating a group of 20 patients, 12 to 20 years of age respectively, affected by node-pulmonary tuberculosis with INH in massive doses of 20 mgr./Kg. daily for a 150 day period.

The degree of pathology varied from minimal and moderate forms to severe involvement featured by wide extension and destruction of the pulmonary parenchyma.

In addition to INH, some hepato-protective drugs were administered to each subject; the starting dose of the drug was 10 mgr./Kg. daily, increasing then to a total of 200 mgr. within a week until a maximal dosage of 20 mgm./Kg. is realized. In no case was the daily dose of 1 gram of INH exceeded. The total mean dose was round 100 gr. of INH per patient.

The drug tolerance generally was very good. A mild icteric syndrome occurred in only two cases after 30-35 gr. of INH had been given. Upon discontinuing therapy, rapid regression of the icterus occurred. In one of these two cases, it was possible to continue treatment to a successful completion without further complications. It should be noted that two of the patients in this series showed rather severe and far advanced pulmonary lesions.

In our opinion, the presence of mild liver disturbances does not contraindicate therapy with INH given in high dosage, but does necessitate very careful follow-up by the attending physician, so that interruption of therapy may be instituted quickly if so indicated and protective therapeutic

measures regarding the liver may be formulated. In fact, in the majority of our cases, the liver function was normal or sub-normal, and in only four patients were slight alterations of liver function noted. These latter quickly returned to normal with simultaneous regression of the tuberculous process.

The clinical results, after five months of therapy, appeared to be quite favorable in nearly all cases, except three. It was noted that in the majority, a significant correlation existed between the state of clinical improvement and the improvement of the local systemic and radiologic picture. However, the concept already held on the basis of experiences of these last few years that a mean therapy of INH in the dosage of 5-10 mgr./Kg. daily is effective treatment in recent forms, even if these latter have ulcerated and disseminated characteristics, is still true, since these forms can revert to a status of clinical recovery. However, in evaluation of the results of the treatment of chronic tuberculosis, the results are less striking. Favorable results in tuberculous lymphadenitis have been observed only towards the end of treatment, at about the fourth or fifth month of therapy.

The accompanying beneficial results are stated; an increase of the body weight in 60 per cent of cases; a decrease of the sedimentation rate in 75 per cent; a skin reactivity to tuberculin tested by the allergometric method was increased in six, reduced in five, and unchanged in nine patients; an increase in nearly all cases of circulating antibodies, tested with the Fenbatticin antigen of Petragnani; no alteration of the hematocrit or peripheral blood picture; negative urinalysis.

Biologic and culture determinations of sputum and gastric samples in the majority of the cases at the beginning of therapy, became negative in three of five positive cases.

Since the drug is well tolerated and its beneficial effects on tuberculous lesions recognized, we might question if this is not an opportune time to change our mode of treatment with isoniazid in a manner utilizing higher doses of 20 mgr./Kg. daily in the usual treatment of tuberculosis in children and young people.

In tuberculosis of new-borns, and of the first two or three years of age, we agree in using 15-20 mgr./Kg. daily, especially in acute progressive phases of the disease, but in grown children and young adults, we do not see the real necessity of always using massive dosages, except for short periods and for particular cases, in which instances we adhere to doses of 8-10-12 mgr./Kg. daily, a recommendation of ours since the initial clinical utilization of isoniazid in 1952-53.

Our clinical and biologic observations testify to the good INH tolerance in high doses by a group of patients (females) affected by tuberculosis at the puberal or postpuberal stage and should support the case for routine treatment in antituberculous prophylaxis.

The second group of investigations is experimental and it repeats in its general features the experiment of Ferebee and Palmer on guinea pigs.

G. Spina and M. Lucchesi carried out the experiment on 320 guinea pigs

of the mean weight of 400 gr., subdivided as follows:

1) 160 animals were infected subcutaneously in the right groin with a virulent strain of M.t. (C.10) suspended in 1 ml. of Dubos medium in the dose of 1/100 mgr. Of these animals, 120 were immediately treated with isoniazid subcutaneously in the daily dose of 7 mgr. per animal (about 19 mgr./Kg. weight), for 75 days, while 40 received no treatment.

2) Another 80 animals were given INH for the same duration and in the same dosage as above, but not infected. This group served as controls, indicating weight behavior, mortality and drug tolerance.

3) 80 animals were not infected nor treated with isoniazid, but stabled in the same conditions as the preceding groups. This group served as controls regarding weight and mortality independent of any treatment.

The remarkable mortality verified in all animals was due to concomitant diseases, pulmonary mostly, except for the infected, untreated controls which, from the end of the first month died principally from a very active form of generalized tuberculosis.

At the end of this first part of the experiment, the surviving animals were subdivided in the following manner:

1) 48 animals of those already infected and treated with INH:
   a) 24 reinfected with the same strain in the dose of 1/1000 mgr. in the left groin (control of the eventual vaccinating power of the primary infection);
   b) 24 animals without any treatment (control of an eventual renewal of primary infection).
2) 32 animals already treated with INH and uninfected:
   a) 16 infected with 1/1000 mgr. of the same strain, suspended in 1 ml. of Dubos medium and given subcutaneously (control of the reinfection behavior of the preceding group, 1 in animals that had already received isoniazid therapy);
   b) 16 infected as above and treated with INH (primary infection in animals given prophylactic therapy with INH).
3) 50 healthy animals:
   a) 25 infected with the same strain and untreated;
   b) 25 infected and treated with INH.

This last group represents a general control of the second part of the experiment.

On evaluating the results of part 1 of this experiment, it was readily discernible from our protocols that animals infected with a virulent strain while under the protection of INH did not present tuberculous lesions in most cases, or only a modest adenopathy of a hyperplastic type at the site of infection. It is a remarkable fact that the cultures of organs from ten animals that had died after 45 days because of the virulent infection were sterile, and that the tuberculin tests were negative or doubtful in 34 cases on 48 animals living on the 75th day after the infection, while in no case was severe positive reaction associated with necrosis observed, as noted in the control animals. The percentages of surviving animals

are altered by the great number of spontaneous deaths occurring in each of the group from intercurrent diseases. However, it is possible to state that by the 75th day from the beginning of the experiment, 48 guinea pigs out of 120 of the infected group treated with INH, survived (40 per cent) ; while only four animals of the control group, infected and untreated, were alive (ten per cent).

So far, it is possible to state that the results of our experiments agree with those performed on guinea pigs by Ferebee and Palmer—even treatment with INH was started the same day that primary inoculation with virulent tubercle bacilli was carried out—and also with those studies carried out on cows.

The results of the second part of the experiment can be summarized as follows:

1) In the animals already infected and treated with INH and then in 75 days reinfected and untreated, a reactivation of the tuberculous disease occurred in some animals, principally during the second month in those lesions produced by the first inoculation. The severity of tuberculosis in these guinea pigs was lower than that of controls infected with the same strain and doses, but which had not previously been infected or had received INH therapy.

2) The infected animals treated with INH for a period of 75 days and not reinfected were used as a study of the eventual relapse of the disease. This led to some interesting observations.

At autopsy, 50 per cent of them did not present signs of active tuberculous disease or lymphatic hyperplasia at the inoculation site. Furthermore, investigation by culture of M.t. carried out at the same time on fragments of the main organs (spleen, liver, and lungs) was always negative. In the other animals, there was an evident relapse of the disease, in which about 20 per cent showed severe lesions and in the remaining, only caseous lymphadenopathies at the inoculation site.

In these guinea pigs, the resistance of M.t. isolated from various organs to INH was also controlled. It was negative for all strains except in one animal, tubercle bacilli of which were resistant to 1 gamma of INH.

The fact that lesions were always more prominent at the inoculation site or only related to this, limits the hypothesis that the infection restarts only at the inoculation site. This is supported by the case of an animal from which positive cultures were obtained only from lymph nodes at the inoculation site, and negative from other tissue sites.

To clarify the results obtained in the above mentioned groups, we can add the following observations: a) the strain we used had an excessive virulence and the dose was still too high for this type of experiment; INH treatment was of too short a duration; b) in the first group, the eventual immunity given by the primary infection was probably masked by the reexacerbation plus the reinfection effect.

We will repeat therefore this series of experiments with less virulent strains and with lower doses to reach the approximate conditions of human pathology.

The third group of investigations carried out by me, L. Praloran and D. Oricchio and co-workers, is concerned with a first attempt of chemoprophylaxis with INH in a wide group of children of both sexes (more than 600) of varying ages, 4 to 11 years, being mostly *skin-positive, but without clinico-radiologic manifestations of active tuberculosis, coming from tuberculous families* or employed in the Forlanini Institute.

The fundamental aim of these investigations was in establishing the individual tolerance to the drug administered in the dosage of 20 mgr./Kg. daily for a six month period; the eventual variation of the tuberculin test and, at the same time, the potential vaccinating capacity of preventive isoniazid treatment, mainly in households infected with tuberculosis. Some of these children were left in their own homes (about 40 per cent) and continued their usual life of study and play; these children came mostly from healthy families, but a minority lived with tuberculous or ex-tuberculous people. Others were sent to a preventorium or college (60 per cent).

The controls were represented by an equal number of subjects put in the same environmental conditions and left untreated.

Before treatment was started, all patients were subjected to the following: physical examination, radiographic and schermographic examination of the chest, weight control, control of the skin reactivity to tuberculin (carried out in 60 per cent of cases with allergometric intradermoreaction and in 40 per cent with wax-taper reaction), examination of the amount of circulating antibodies, of sedimentation rate, eosinophils in blood and urine; in some cases, liver function tests before and during the period of treatment. Each subject was given a clinical report with a summary note and a second report in which were daily noted the amounts of isoniazid therapy established in that particular case and routes of administration. The cases were carefully controlled in their followup by a group of expert social assistants and, at intervals, by the doctor. The results obtained from the various preliminary investigations can be summarized as follows:

The radiologic examination, excluding a minority of cases where it was not possible to detect any pulmonary alteration, showed predominately signs of progressive infection in the form of hilar calcifications, parenchymal calcific foci, enlargement of the hilar shadows without perifocal reaction, and alteration of the bronchovascular markings corresponding to the parahilar regions. The tuberculin reaction, which was positive in 87 per cent of cases examined with intradermal infections in gradual doses and in 60 per cent of those examined with allergometric wax-tapers, showed in general a good relationship to the pulmonary radiologic findings. Circulating antibody determination was negative in most cases, the erythrocytes sedimentation rate was normal; slight eosinophilia was noted in some cases; urinalyses were negative.

In consideration of the youthfulness of our subjects and the lengthy period of treatment, the following particular preparations were made up and utilized in an effort to make the drug more agreeable. The ordinary tablet and syrups were also utilized:

chocolates with 50 and 100 mgr. of isoniazid
fruit jelly with 50 and 100 mgr. of isoniazid
biscuits with 50 mgr. of isoniazid

Vitamins, especially of the B complex, were given either in a combined form as a syrup preparation, or singly. The difficulties encountered in carrying out such a therapeutic program on a large scale were apparent to us in that while easily surmountable for groups of subjects living in preventoria or colleges, it is much more difficult for groups of patients treated at home. It is difficult to convince the relatives of these relatively asymptomatic patients to permit their children to undergo diagnostic procedures in spite of lectures, explanatory sessions, and that allergometric controls and therapy were new to them.

The figure of 600 patients to which our present observations are pertinent, immediately suffered a sharp loss for the above-mentioned reasons. It is to be hoped that in time a more wide-spread knowledge of the reasons for this research will eliminate these difficulties.

In 50 per cent of the patients, chemoprophylaxis has been given for a period of four months, while in the other 50 per cent, it has been given for two months. It is difficult to speak of our results at this time, since their true value can only be evaluated in the years to come. At the present time, our observations have to be limited to modes of administration, drug tolerance, the influence on general and local conditions, the allergic tuberculin modifications, variations of the amount of circulating antibodies and to other laboratory data. The drug has been administered starting with an initial dose of 10 mgr./Kg. daily, followed by an increment of 5 mgr./Kg. daily each week, until a dosage of 20 mgr./Kg. daily is attained. In no case has a daily dosage of 800 mgr. been exceeded.

Sometimes one has considered it convenient to administer special preparations (fruit jelly, chocolates and biscuits) to small children, while the drug was given in tablets or syrups to older children. For a child weighing 20 kg., the drug was divided during the day in the following manner: 2 biscuits of 50 mgr. of isoniazid each, in milk at breakfast; 1 teaspoon of syrup containing 100 mgr. of isoniazid after lunch; 1 chocolate of 100 mgr. for lunch; 1 teaspoon of syrup of 100 mgr. after dinner.

The drug tolerance was excellent in nearly all cases in regard to both the daily and the total doses. In only four of 600 patients was it necessary to discontinue treatment (0.66 per cent), two because of a relapsing dermatitis, and two because of gastroenteritis. These findings are in complete agreement with what has been observed by pediatricians in recent years and with our own recent investigations on tuberculosis in young people, and it supports the logical assumption that very young subjects not presenting active tuberculous lesions have a physiological integrity of body functions which is not encountered in older subjects or carriers of active tuberculosis.

The clinical improvement in nearly all cases examined was mainly featured by increase in body weight.

We cannot discuss certain local improvements in view of the fact that

patients examined by us did not present pulmonary alterations capable of showing recent modifications. In general, these patients were categorized as chronic, manifesting either localized pulmonary or multiple tracheobronchial lymph node calcifications.

Possible modifications or alteration of the tuberculin test by allergic factors was controlled by us, in that only 100 patients were tested in an effort to avoid the possible occurrence of a negative test because of desensitization consequent to repeated cutaneous testing. An analysis of the results furnished by this controlled study on these 100 patients was brought about by pre- and post-therapy evaluation to determine degree of reactivity in light of desensitization factors.

In the 100 patients followed by controlled intradermal testing, a nearly equal number of increased, stationary, or decreased degrees of reactivity were noted. To date, negative reactions have not been observed. It was not possible to evaluate the variations in total circulating antibodies now in the sedimentation rate; a moderate eosinophilia in the peripheral blood of some patients was noted. Urinalyses were negative.

Conclusions

On the basis of the above reported data, we can state that prophylactic treatment based on the administration of high doses of isoniazid can be carried out without trouble in tuberculin positive or negative subjects, not presenting with specific, active pulmonary lesions. From the point of view of prophylaxis, it would be interesting to follow up, in a careful manner, the group of skin-positive or negative children living in infected households, during or after the interruption of treatment with isoniazid.

Final Considerations

From this brief review of experimental findings in animals and of observations made in man, can certain theoretical postulates suggest and support the new concept of an anti-tuberculosis chemoprophylaxis by means of isoniazid? Or is this statement premature and are further investigations necessary before the practical application can proceed?

In our opinion, an important fact uniting the different experiments carried out already exists: INH administration in opportune doses and in a continuous way to an animal exposed to a massive contagion or to a virulent inoculation prevents the development of a disseminated tuberculous infection during the time of administration of the drug. The drug appears to block multiplication of the bacilli within the primary focus.

Does one obtain sterilization of the pre-existing foci?

Even admitting that the drug administered in high doses develops a bacteriocidal action—except in some rare cases—the demonstration of total extinction of tuberculous foci on the basis of bacteriologic and histologic examinations has not been shown. It is, however, probable—in view of the reported observations—that bacilli, persisting in lymph nodes, spleen, and in other organs, may lose a good deal of their virulence (perhaps through a mechanism of transformation into catalase-negative INH-resistant bacilli) so that after cessation of drug therapy, they can no more cause renewal of localized activity or endogenous re-infection.

Does INH treatment increase the resistance of the organism to a new exogenous infection?

To this fundamental question, we may give an affirmative answer with certain reservations referable to a recent article by Dubos and principally because of that possibility that coexistence in the same organism of attenuated and virulent strains may take place. The experiments of Ferebee and Palmer on guinea pigs revealed that isoniazid increases organ resistance even when therapy is interrupted for many weeks. Similarly, the experiments of others appear to confirm the vaccinating power of INH-resistant strains against a virulent infection, being very similar in its allergic and pathologic features to that of BCG vaccine, in a manner demonstrated by the original investigations of the Italian schools of veterinary medicine who described the high degree of resistance against tuberculosis, wherein calves had been protected by suitable isoniazid treatment. The last question is concerned with the drug toxicity and if the drug is administered for a long term and in high doses.

We have already seen that toxic effects, even in the dosage of 25 mgr./Kg. daily in guinea pigs are almost nil, and that in calves and domestic animals, doses of about 10 mgr./Kg. daily are well tolerated. Only Badiali has observed an increased loss of weight in calves treated with INH, which he attributes—but without proof—to toxic drug effects. In humans, pediatricians have already demonstrated the excellent tolerance by tuberculous children of infant and junior age to high doses of INH. It has also been pointed out that doses of 20 mgr./Kg. INH daily are well tolerated, with a few exceptions in adolescents who have progressively active tuberculosis, also in clinically healthy children undergoing a therapeutic prophylactic regimen with isoniazid.

In summary, drug toxicity has to be considered practically nil even in relatively high doses for long periods of administration (four - six months). We feel that in spite of many uncertainties that exist, the theoretical and experimental observations to date serve to indicate that an experiment of isoniazid chemoprophylaxis on a large scale, on men and cows, should be undertaken. Objections could arise as to the necessity of such a program, in view of the present-day status of tuberculosis.

It is undeniable—as Debre made evident at the Paris meeting in December, 1955—that there are some nations—such as Sweden, Denmark, U.S.A., Canada, etc.—where the problem of tuberculosis in children does not constitute social danger and where primary tuberculous infections are in a minority. It is not necessary in these countries to start an anti-tuberculosis vaccination on a large scale, or to institute a chemoprophylaxis regimen, but it would suffice, as Walgreen of Stockholm maintains, to start treatment early in those relatively few cases of active tuberculosis occurring in the first three years of life and before the age of puberty.

But Italy, France, West Germany, and England do not enjoy this happy state of affairs! Therefore, even today, all those means of specific and non-specific prophylaxis, well known in the secular history of the fight against tuberculosis, are necessary! Here in Italy, for example, the frequency

curves of primary tuberculosis infections—in a clinically inactive phase and in an evolutionary phase—are very high in infants and children of school age, as well as in military recruits.

The investigations of Giovanardi and Parvis of Boffa, Luzzatti, Grattarola and Calamari, in the pre-isoniazid period of 1950-52, studied 189,275 children and pupils from 3 to 15 years of age (the majority from Northern Italy, especially Lombardy, and a minority from central and southern Italy) by means of the wax-taper tuberculin reaction, and obtained the following results: at six years of age, the tuberculin index remains rather low, ranging around an average of 11.3 per cent, increasing gradually to 28.4 per cent in children 12 to 15 years of age, and rising in some cities as Bologna and Trieste, to more than 30 per cent. It is to be noted, furthermore, that the positivity of the wax-taper reaction is lower than that of the intradermal test, and therefore, one has to assume that the percentage of primary tuberculous infections is higher than registered.

An insufficient number of military personnel have been studied to date, so that statistical data are not accurate enough for appraisal of the tuberculin reacting population of the country.

The investigations of M. Clemente and R. Lo Schiavo carried out on 3,000 Navy men by means of skin and wax-taper reaction, utilizing the antituberculin of Petragnani, give 47.7 per cent positive results. Therefore, we feel very secure in stating that about 50 per cent of the adult Italian population at the present time is not free from tubercle bacilli contamination.

Perhaps with the advent of isoniazid, the situation has improved in recent years, manifested by a sudden lowering of the mortality rate in all civilized countries? We are not so optimistic, however, about the mortality rate because, unfortunately, schermography is still not very highly developed, the same being true of preventoria organization and the systematic removal of infants from infected foci. The hospitalization of many "open" cases of tuberculosis is delayed and avoided by patients who believe that they can be just as easily treated at home, while undergoing an irregular, incomplete, and sometimes incongruous mode of chemotherapy.

Therefore, we are convinced that a specific prophylaxis—by vaccination or chemotherapy—at least for the course of one generation, is to be recommended in Italy, in addition to the utilization of nonspecific aids, if we want to approach or better the results of other nations. Here arises the crux of the problem: antituberculous vaccination or chemoprophylaxis? Or both of them?

In a recent article, G. Canetti proposed combining vaccination with isoniazid chemoprophylaxis; he postulated utilizing an INH-resistant BCG strain for vaccinations. Justification of his proposal lies in the following considerations: BCG vaccination gives a specific antituberculous resistance only after a certain time, usually longer than the anti-allergic period and varying two to four months. During this period, the child, if not immediately removed from the source of infection, can incur a severe tuberculous infection; at this time, the objective in mind would be to administer isoniazid to each vaccinated individual for a period of three-four months, a

period during which specific resistance is developing. These individuals would not be removed from the infecting source.

However, G. Canetti voices certain objections, namely: that the BCG vaccinating power—like that of any living attenuated vaccine—is related to the potential ability of inoculated bacilli to develop immunologic reactivity in the host organism (upon this subject, see the investigations of Monaldi and of his school). This reason, according to the French author, accounts for the greater degree of specific resistance developed by BCG than that provided by an inoculate of dead tubercle bacilli.

Now, if isoniazid is administered to a patient recently vaccinated, BCG multiplication, sensitive to isoniazid action, will be inhibited; therefore, the maximum degree of specific resistance against tuberculosis that should be evident after vaccination will not be obtained. In consideration of this, the thought occurred to us of vaccinating children with an INH-resistant BCG strain. This can be done because BCG has resistant "mutants" to the drug, and therefore, by careful selection, a BCG vaccine, completely INH-resistant, may be obtained.

Following the above-mentioned procedure, according to Canetti, the problem of vaccination and chemoprophylaxis should be resolved, thus enabling adequate protection against virulent re-infection occurring in the child.

The other objection of Canetti is bacteriological in nature. Thus, when the BCG strain has become INH-resistant and catalase-negative, it has lost the potentiality of multiplying in the host organism. However, in circumstances as this, will the attenuation remain permanent, or will there be a possible re-establishment of virulence? That this occurs, has been recently shown by G. Petragnani in a systematical series of investigations of BCG cultured on his medium with a tensioactive substance. It may be possible that such an INH-resistant, but catalase-positive strain may also have many virulent bacillary variants, as has been widely shown also by the investigators of the Forlanini Institute. The attractive proposal of the famous French bacteriologist, therefore, can be objected to on the basis of the bacteriological problem, the great technical difficulties in manufacturing such a vaccine, completely stabilized and permanently attenuated. In any event, tentative consideration must be given to the idea of combining chemoprophylaxis and antituberculous vaccination, so as to complete the action of the first with that of the second, especially in those countries where BCG vaccination is widely used and psychologically accepted. Also, the possible combination of chemoprophylaxis and antituberculous vaccination with dead bacilli (Petragnani's vaccine).

And what about subjects being in the same contagious environment, but already skin-positive?

In regard to this, we are not able to adhere to the concept of A. Assis, Rosenberg, Silveira and of the Brazil School of Phthsiology, namely: that of "concurrent vaccination," not only in skin-negative subjects, but to everybody without distinction, whether tuberculin-positive or negative. We believe that further inoculation of bacteria (living, attenuated, or

dead) of these skin-positive subjects already exposed to a new outside contamination, does not add any immunological benefits, and further, we do not relish the introduction of tuberculin material that may stimulate and reactivate the foci of primary infection (see the experiments of C. Pana and co-workers).

In view of the present clinical and social conditions, we believe it is important to realize that simple isoniazid chemoprophylaxis with the above-mentioned modalities, which on one hand will exert immediate therapeutic action against existent tuberculous foci within lymph nodes, and other organs, on the other hand, will furnish through the INH-resistant mechanism or some other mechanism, a greater resistance against an endogenous or exogenous re-infection.

Thus, we think it is important in such living conditions as we have already stated, to repeat isoniazid treatment at appropriate intervals during the second and third year, especially if the patients concerned are infants, born of tuberculous parents (see the preliminary plan).

The objection by some that protection given by INH lasts only during the administration period may be satisfied by experimental data collected to date, showing a lasting defense even after treatment is discontinued. This important problem will be completely solved only by future experience.

The hesitancy of developing, in these children, an INH-resistance that could cause trouble in the future in the event of the development of a post-primary tuberculosis, can be dispelled to some extent with the advent of new chemoantibiotics such as cycloserine—that supplement other well-known chemoantibiotics and facilitates the treatment of active tuberculosis.

Utilization of isoniazid chemoprophylaxis has been recognized, as we have seen, by some illustrious Italian colleagues of veterinary medicine in the fight against bovine tuberculosis and I am convinced that good results can be obtained, following the scheme we have established for man, with variations naturally imposed by the differences of species and living conditions.

This new prophylactic program against pediatric tuberculosis can be successful, or even subsequently improved dependent upon future advances in phthisiology or therapy. It is our opinion that this program has practical value in spite of the inherent difficulties that seem to be present. The latter, we feel, may be overcome in Italy by means of publicity, much more easily than in the case of vaccination.

Our experiment is continuing and we will evaluate the first results only in the years to come. In any respect, we shall pursue this line of investigation in extending isoniazid chemoprophylaxis treatment through the channels of dispensoria to family groups or other groups strongly contaminated by tuberculosis.

SUMMARY

1. The author starts with the assumption that at the present moment, in the antituberculosis fight in Italy, it is necessary—at least for the length of one generation—to perform *specific prophylaxis* in addition to

non-specific prophylaxis. This gives rise to the problem: antituberculous vaccination or chemoprophylaxis? The author favors the second course of action and especially the institution of chemoprophylaxis using high doses of isoniazid (20 mgr./Kg. daily) in skin-positive infants and children if living in tuberculous households. He reports and analyzes various experiments carried out in the United States and at the Forlanini Institute of Rome, and experiments carried out on calves by workers at Perugia University which uniformly prove that isoniazid administered under proper conditions is able to protect subjects from a massive infection and to confer upon them an increase of resistance against the tubercle bacilli comparable to that by means of vaccination with BCG.

2. The author feels that there is sufficient experimental basis for utilizing this system of prophylaxis in man. He has widely publicized the investigations going on in Rome, pointing out the excellent tolerance to the drug, even though given for a long period and in high doses to children, and the practical possibility of instituting a program of prophylaxis with isoniazid in cases of tuberculin positive individuals who do not have clinically detectable tuberculosis. This experiment in man (which, in addition to that announced by Debre in Paris, is the first in world medical literature) to date deals with 600 children under treatment for a period of six months while living either at home with tuberculous relatives or in preventoria and antituberculosis colonies. The drug was administered in the dosage of 20 mgr./Kg. daily in the form of lozenges, syrups, jello, chocolates, or isoniazid biscuits, and was perfectly tolerated.

3. The author discusses Canetti's proposal of combining chemoprophylaxis with vaccination using for the latter a BCG strain, INH-resistant and catalase-positive. He concludes that such a program would be difficult to put in practice and would carry with it a certain danger. A tentative scheme of treatment with INH for prophylactic purpose is proposed according to whether the skin-positive children involved are in a contagious or non-contagious environment. Finally, the author believes that a program could also be applied in the fight against bovine tuberculosis, thus protecting calves living in infected stables, adhering fundamentally to the regimen utilized in man with variations normally imposed by the difference of species and environment.

RESUMEN

1. Empieza el autor por asentar que en el momento actual en la lucha contra la tuberculosis en Italia es necesario, por lo menos durante una generación, llevar a cabo medidas de *profilaxis específica* adenmás de la *profilaxis no específica*. Esto hace plantear el problema de la vacunación antituberculosa o la quimioprofilaxis.

El autor se inclina por la segunda y especialmente por el uso de la isoniacida a dosis altas (20 mgrs. por Kg. diariamente) en los tuberculinopositivos en ambiente familiar tuberculoso. Relata y analiza varios experimentos llevados a cabo en los Estados Unidos y en el Instituto Forlanini en Roma así como los experimentos en terneras hechos en la Universidad

de Perusa que de manera uniforme demuestran que la isoniacida administrada adecuadamente, protege a los individuos de la infección masiva y les confiere una resistencia aumentada contra el bacilo de la tuberculosis comparable a la obtenida por el BCG.

2. Cree el autor que hay una base suficiente de carácter experimental para usar este procedimiento en el hombre. Ha dado publicidad amplia a las investigaciones en Roma señalando la excelente tolerancia de la droga aunque se dé por largo tiempo y en altas dosis en los niños y la posibilidad práctica de instituir planes de profilaxis con isoniacida en casos de individuos tuberculinopositivos que no tienen tuberculosis evidente clínicamente. Este experimento en el hombre (que además del de Debre en París, el el primero en la literatura médica) incluye hasta ahora a 600 niños bajo tratamiento por un período de seis meses aunque convivan con tuberculosos en sus hogares o en preventorios o en colonias antituberculosas. La droga se ha administrado a la dosis de 20 mgrs. por Kg. diariamente en forma de grageas, jarabes, jaleas, chocolates y galletas de isoniacida y fué perfectamente tolerada.

3. El autor discute la proposición de Canetti de combinar la quimioprofilaxis con la vacunación usando para ésta una cepa de BCG isoniacida-resistente y catalasopositiva. Concluye que tal plan sería difícil de llevar a la práctica y acarrearía cierto peligro. Se propone un esquema de tratamiento a manera de tentativa dependiendo de si los niños tuberculinopositivos se encuentran en medio contagiante o no. Finalmente, el autor cree que un programa podría aplicarse también a la lucha contra la tuberculosis, bovina, protegiendo así a las terneras que viven en establos infectados adhiriéndose fundamentalmente al régimen usado en el hombre con variaciones dependientes de las diferencias en el medio y en las especies.

ZUSAMMENFASSUNG

1. Der Autor beginnt mit der Versicherung, dass es zum gegenwärtigen Zeitpunkt bei der Tuberkulosebekämpfung in Italien norwendig ist, mindestens für die Dauer einer Generation eine *spezifische Prophylaxe* zusätzlich zur *unspezifischen Prophylaxe* durchzuführen. Damit entsteht das Problem: Tuberkuloseschutzimpfung oder Chemoprophylaxe? Der Autor bevorzugt den zweiten Weg des Vorgehens und besonders die Einrichtung der Chemoprophylaxe unter Verwendung hoher Dosen von INH (20 mg-kg tägl.) bei tuberkulinpositiven kleinen und grösseren Kindern, falls diese in tuberkulösen Haushalten leben. Er berichtet über verschiedene Experimente und analysiert sie, die ausgeführt wurden in den USA und am Forlanini Institut in Rom, und Experimente, die an Rindern von Mitarbeitern der Universität von Perugia ausgeführt wurden und die einheitlich beweisen, dass unter geeigneten Bedingungen verabfolgtes INH im Stande ist, Personen gegen eine massive Infektion zu schützen und ihnen eine erhöhte Resistenz gegen die Tuberkelbazillen zu verleihen, vergleichbar derjenigen, die mittels BCG-Impfung erzeugt wird.

2. Der Autor hat die Überzeugung, dass eine ausreichende experimentelle Grundlage vorliegt für die Nutzbarmachung dieses Systems von Prophylaxe

beim Menschen. Er hat im ausgedehnten Masse die in Rom unternommenen Untersuchungen veröffentlicht unter Hervorhebung der ausgezeichneten Verträglichkeit des Mittels, auch wenn es Kindern für lange Zeit und in hohen Dosen gegeben wird, und die praktische Möglichkeit zur Einführung eines Programmes der Prophylaxe mit INH in Fälle von tuberkulinpositiven Individuen, die keine klinisch feststellbare Tuberkulose haben. Dieser Versuch beim Menschen, (der unter Hinzunahme des von Debre in Paris angekündigten, der erste in der medizinischen Weltliteratur ist) hat zu tun mit 600 Kindern, die für eine Zeit von 6 Monaten in Behandlung stehen, während sie entweder zu Hause mit ihren tuberkulösen Verwandten leben oder in Präventorien und Antituberkulösen Kolonien. Das Mittel wurde in der Dosierung von 20mg-kg.Tägl. verordnet in Form von Tabletten, Syrup, Schokolade oder INH-Biskuits und wurde gut vertragen.

3. Der Autor diskutiert Canetti's Vorschlag der Kombiantion der Chemoprophylaxe mit der Impfung unter Verwendung eines INH-Resistenten und Catalase-positiven BCG-Stammes dafür. Er folgert, dass ein solches Program schwierig in die Praxis umzusetzen ist und eine gewisse Gefahr mit sich bringt. Es wird ein probeweises Schema der Behandlung mit INH für prophylabtische Zwecke vorgeschlagen, je nach dem die beteiligten hautpositiven Kinder in einer ansteckenden oder nicht ansteckenden Umgebung leben. Schliesslich spricht der Autor die Überzeugung aus, dass auch im Kampf gegen die Rindertuberkulose ein Program zur Anwendung gebracht werden könnte, um auf diese Weise Rinder zu schützen, die in infizierten Ställen leben unter grundsätzlicher Verfolgung der beim Menschen genutzten Methode mit Abwandlungen, die normaler-weise durch die Differenzen von Rasse und Umgebung bedingt sind.

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Depressed Response to Intravenous Sympathicomimetic Agents in Humans During Acidosis

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Since the Spring of 1954, total cardiac by-pass has been employed at the University of Minnesota Hospitals in order to correct various intracardiac defects under direct vision. A common denominator of the various pump-oxygenator systems which have been used is the low flow or azygos flow principle. Diminished tissue perfusion during azygos flow leads to metabolic acidosis, which can be compensated or masked by appropriate hyperventilation of the oxygenator with resultant respiratory alkalosis.[1] Some patients have exhibited persistent heart block and/or hypotension postoperatively, and at times this hypotension has been irreversible.

What is the evidence for the co-existence of shock and acidosis? In 1918, Cannon[2] championed the use of alkali in the treatment of shock, but his suggestion was refuted the same year.[3] Burget and Visscher[4] reported that the adrenalin response of the vascular system of the pithed cat could be made to vary by varying the pH of the blood, and they found from pH 6.9 to 8.0 the response progressively increased. Levine et al[5] found that intravenous alkali increased the survival rate of dogs subjected to prolonged hemorrhagic shock (that is, the duration of shock was prolonged until the carbon dioxide capacity of the plasma fell to or below 15 volumes per cent). More recently Page and Olmsted[6] demonstrated that the pressor action of adrenalin and noradrenaline was diminished in dogs subjected to respiratory acidosis.

We have repeated and extended these earlier observations in the experimental laboratory; and we have tested and applied these findings in healthy human subjects and in clinical patients respectively.

Methods

I. Healthy human subjects: Two non-anesthetized male subjects were given small doses of epinephrine intravenously under conditions of eupnea, respiratory acidosis and voluntary hyperventilation. Arterial blood pressure was recorded with a pressure transducer which was connected to a No. 15 needle positioned in the subject's brachial artery. One channel of a two-channel direct writing oscillograph was used to record systemic arterial blood pressure, and electrocardiographic records were obtained on the second channel. Respiratory acidosis was produced by inhalation of 10 per cent CO_2-90 per cent O_2 gas mixtures, and respiratory alkalosis was produced by voluntary hyperventilation. Minute respiratory volumes were

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measured by the open circuit method using a modified, tightly-fitting A-15 Army Aviation mask and collecting the exhaled air in a 100-liter balanced spirometer. Subjects noted no resistance to breathing with this system except at very high rates of flow, i.e. 60 to 80 liters per minute.

Blood samples were drawn through the brachial artery needle into oiled, heparinized syringes, and arterial blood pH determinations were made under anaerobic conditions at a temperature of 37° C with a glass electrode.[7] Total carbon dioxide content determinations were made on arterial blood plasma with a Van Slyke and Neill manometric apparatus. Carbon dioxide tension, carbonic acid concentration, and bicarbonate concentration were calculated from arterial blood pH and plasma total carbon dioxide content values, utilizing the Henderson-Hasselbalch equation.

II. Clinical patients: Six patients in shock who were refractory to intravenously administered pressor drugs were studied. Systemic arterial pressure was recorded through an intra-arterial (brachial or femoral) needle in three patients and cuff pressures were obtained periodically in the other three patients. Arterial blood samples were drawn for blood pH determinations and either arterial or venous blood was used for carbon dioxide combining power values. Molar sodium lactate was administered into an antecubital or forearm vein in an attempt to restore the blood pH towards normal levels. As the arterial blood pressure returned to the patient's normal level, the administration of pressor drugs was diminished or discontinued.

Results

I. Healthy human subjects: The results of arterial blood studies and minute respiratory volume in two healthy subjects under conditions of eupnea, respiratory acidosis, and repiratory alkalosis appear in Table I.

In subject R. C. at pH 7.36, ¼ cc of 1:10,000 intravenous epinephrine produced a change in heart rate from 60 to 114 per minute. The same amount of intravenous epinephrine during respiratory acidosis (pH 7.25) elevated the heart rate from 114 to 138 per minute. The dose of intravenous epinephrine was halved at pH 7.61, and during this state of respiratory alkalosis ⅛ cc of 1:10,000 epinephrine accelerated the heart rate from 114 to 156 per minute. Subject N. C. showed the following changes in heart rate at three different blood pH levels following 0.3 cc. of 1:20,000 intravenous adrenalin. During eupnea at pH 7.38 the heart rate changed

TABLE I

ARTERIAL BLOOD AND MINUTE VOLUME STUDIES IN HUMANS DURING EUPNEA, RESPIRATORY ACIDOSIS, AND RESPIRATORY ALKALOSIS

	Subject	Arterial Blood pH	Alveolar pCO_2 (mm.Hg.)	H_2CO_3 (mEq/L)	$BHCO_3$ (mEq/L)	Minute Resp. Volume (liters)
Eupnea	R. C.	7.36	48	1.4	25.4	5.9
	N. C.	7.38	45	1.4	25.1	6.0
Resp. Acidosis	R. C.	7.25	66	2.0	27.4	54.3
	N. C.	7.22	75	2.2	29.1	91.3
Resp. Alkalosis	R. C.	7.61	21	0.6	20.0	48.0
	N. C.	7.60	22	0.7	20.6	86.8

from 60 to 96 beats per minute after adrenalin, during respiratory acidosis at pH 7.22 the cardiac rate changed from 90 to 96 beats per minute following adrenalin, and during respiratory alkalosis at pH 7.60 the heart rate accelerated from 102 to 114 beats per minute after adrenalin. Perhaps the most alarming change in subject N. C. was the appearance of ventricular extrasystoles and the transient absence of T waves following intravenous epinephrine during respiratory alkalosis.

II. Clinical patients: Laboratory data in clinical patients were incomplete. The patients studied had hypotension and septicemia, and all of the patients were receiving intravenous pressor agents prior to our studies. In spite of large doses of pressor agents the arterial blood pressure of these patients was 40 to 60 mm. of mercury.

The largest maintenance dose of pressor agents which any of these patients were receiving was 500 mgm. of metaraminol (aramine) in 500 cc. of five per cent dextrose at an infusion rate of 22-28 drops per minute. Arterial blood pH samples were drawn and the lowest blood pH was 7.06. The lowest value for carbon dioxide combining power in blood samples from these patients was 9 mEq./L. Molar sodium lactate (300-1000 cc.) was administered intravenously to these patients and the highest blood pH obtained following this therapy was 7.51. During and following the intravenous administration of molar sodium lactate, the blood pressure returned towards a normal range even though the intravenous pressor agents were diminished or discontinued. Although two of the patients lived for four and eleven days respectively after a hypotensive episode which was refractory to all measures other than intravenous alkali, none of the patients survived.

Discussion

Apparently the pressor and ECG responses to epinephrine and metaraminol are lessened in the presence of acidosis. Metabolic acidosis develops fairly rapidly in shock, and this acidosis can be corrected only by adequate tissue perfusion.

Excellent clinical examples of a rapidly reversible metabolic acidosis are patients subjected to intra-cardiac surgery under a low flow pump-oxygenator system. Arterial blood pH values as low as 7.09 were obtained in patients upon completion of the cardiac by-pass; and within thirty minutes the arterial blood pH had returned to 7.35 to 7.41. On the other hand, if the patients remained severely hypotensive after the cardiac by-pass, metabolic acidosis persisted. Under the latter condition, molar sodium lactate was administered via the intravenous and/or the intracardiac route, and many of these patients recovered. We have also used intracardiac or intravenous molar sodium lactate in treatment of bradycardia and heart block as suggested by Bellet et al[8] with encouraging results.

The problem of acidosis is at times an important factor in a hypotensive patient. The correction of acidosis has at least temporarily reversed what was apparently irreversible shock in the clinical patients studied. In the treatment of shock, a normal blood pressure is not the sole objective. The objective is adequate tissue perfusion. Vasoconstrictor drugs may re-

store a normal blood pressure by means of arteriolar constriction, and yet further decrease tissue perfusion and thereby perpetuate metabolic acidosis. The primary treatment in shock is directed towards a balance between blood volume and capacity of the vascular system in order to increase blood pressure without lowering peripheral blood flow. However, in the presence of metabolic acidosis, intravenous alkali may be a helpful therapeutic adjunct.

The clinical patients reported in this study all had septicemia, intra-abdominal abscesses, etc.; and in spite of partial or complete correction of the metabolic acidosis, the response to intravenous alkali was temporary. However, in asthmatics who have become adrenalin resistant, intravenous alkali has restored their pH towards a normal level, and subsequent injections of adrenalin in these patients have terminated asthmatic attacks.[9]

SUMMARY

1. Healthy human subjects were given intravenous epinephrine during eupnea (blood pH 7.37), during 10 per cent carbon dioxide inhalation (blood pH 7.23), and during voluntary hyperventilation (blood pH 7.61). Arterial pressor and ECG changes following identical doses of epinephrine were minimal during acidosis and maximal during alkalosis. During respiratory alkalosis one subject exhibited ventricular extrasystoles and transient absence of T waves following epinephrine.

2. Clinical patients with septicemia and shock who had become refractory to pressor agents were studied. During this refractory period, arterial blood studies revealed severe metabolic acidosis with arterial blood pH as low as 7.06. Following the partial or complete correction of this acidosis by intravenous administration of molar sodium lactate, blood pressure response to sympathicomimetic agents increased.

RESUMEN

1. Se administró epinefrina intravenosa a personas sanas durante eupnea (pH en sangre 7.37) en tanto que inhalaban dióxido de carbono (pH sanguíneo 7.23) y durante la hiperventilación voluntaria (pH sanguíneo 7.61). Los cambios de presión arterial y los del ECG después de dosis idénticas de epinefrina fueron mínimos durante ácidos y máximos durante alcalosis. Durante la alcalosis respiratoria, un sujeto tuvo extrasítoles ventriculares y ausencia transitoria de las ondas T después de epinefrina.

2. Clínicamente, los enfermos con septiciemis y shock que se han vuelto refractario a los agentes presores, se estudiaron. Durante este período refractario los estudios de la sangre arterial revelaron una severa acidosis metabólica con pH arterial tan bajo como 7.06. Después de la corrección parcial o completa de esta acidosis por la administración de lactato de sodio, molar, la respuesta de la presión sanguínea a los agentes simpaticotónicos aumentó.

RESUME

1. Les auteurs ont injecté de l'épinéphrine par voie intraveineuse chez des sujets sains, au cours de la respiration normale (ph sanguin: 7,37)

pendant l'inhalation de 10% d'oxyde de carbone (ph sanguin: 7,23) et pendant l'hyperventilation volontaire (ph sanguin: 7,61). Les modifications de la pression artérielle et de l'électrocardiogramme avec des doses identiques d'épinéphrine furent faibles pendant l'acidose, et importantes pendant l'alcalose. Un sujet en alcalose respiratoire, fut atteint d'extrasystoles ventriculaires, et présenta une absence transitoire des ondes T après usage d'épinéphrine.

2. Les auteurs étudièrent des malades atteints de septicémie et de shock, qui étaient devenus insensibles aux agents presseurs. Pendant cette phase réfractaire, des études du sang artériel montrèrent une acidose métabolique grave, avec un ph du sang artériel descendant jusqu'à 7,06. Après correction partielle ou complète de cette acidose par administration intraveineuse de lactate de soude, la réponse de la pression sanguine augmenta sous l'influence des agents sympathicomimétiques.

ZUSAMMENFASSUNG

1. Gesunde menschliche Versuchspersonen erhielten Epinephrin intravenös während normaler Atmung (Blut-ph 7,35), während Einatmung von 10% CO_2 (Blut-ph 7,23) und während freiwilliger Hyperventilation (Blut-ph 7,61). Atterieller Druck und EKG-Veränderungen nach identischen Dosen von Epinephrin waren minimal während der Azidose und maximal während der Alkalose. Während der respiratorischen Alkalose wies eine Person ventrikuläre Extrasystolen auf und vorübergehendes Fehlen der T-Zacken nach Epinephrin.

2. Es wurde stationäre Fälle untersucht mit Septikaemie und Schock, die gegen Blutdruckerhöhende Mittel refratär waren. Arterielle Blutuntersuchungen während dieser refraktären Periode ergaben schwere Stoffwechsel-Azidose mit Erniedrigung des arteriellen Blut pH bis auf 7,06. Im Anschluss an die partielle oder komplette Korrektur dieser Azidose durch intravenöse Verwendung von molarem milchsaurem Natrium nahm die Reaktion des Blutdrucks auf sympathikomimetische Stoffe zu.

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The Tuberculin Test as a New Approach to the New Era of Tuberculosis Control*

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In the past two decades great progress has been made in the treatment of tuberculosis. The discovery of potent antituberculosis drugs and the advances in thoracic surgery have brought about a dramatic decline in the death rate from tuberculosis. Such accomplishment certainly can be viewed with pride and satisfaction. However, while much has been achieved in preventing death due to tuberculosis, not nearly as much has been accomplished in preventing sickness. Even in the United States today, new cases of tuberculosis are being reported at the rate of 100,000 per year and this figure does not include those patients who are not being reported to the health authorities. This disheartening fact stands out in spite of the tremendous progress against tuberculosis that has been made in recent years.

A survey of the cases reported reveals that the majority of them were diagnosed in the advanced stages of the disease. This fact is worthy of our attention, because failure of early diagnosis is an important cause of treatment failure today. The potent antituberculosis drugs now available have made the cure of early cases easy. On the other hand, once the disease is allowed to advance to late stages such factors as drug resistance, persistent cavities and necrotic residuals become great hindrances to the success of treatment. From the public health standpoint the advanced cases are responsible for the spread of tuberculosis to healthy individuals. As will be shown later, child after child and family after family are infected by unrecognized or uncontrolled cases of pulmonary tuberculosis. Therefore, from the clinical standpoint, the present method of tuberculosis control is inadequate since too often it fails to find tuberculosis in its early stage. From the public health standpoint, the present method of tuberculosis control is also inadequate because too often it fails to prevent the spread of the infection to healthy individuals. In this paper two aspects of tuberculosis control will be discussed; first, what can be done to prevent the infected from getting sick and second, the early diagnosis of tuberculosis and prevention of infection by an improved case finding technique.

What Can Be Done to Prevent the Infected from Getting Sick?

To answer this question it is essential to know how tuberculosis begins in the human body, what course it takes and where along this course the

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infection can be checked to prevent it from evolving into manifest disease. The formation of the primary complex following the initial penetration of tubercle bacilli is well known. However, the story of primary tuberculosis does not end at this point, for soon after the infection begins there follows a generalized dissemination of the bacilli, with seeding in various tissues of the body. It should be emphasized that this initial dissemination of tubercle bacilli occurs before the tuberculin reaction becomes positive.[1] Recent studies with P^{32} labelled tubercle bacilli have shown that the dissemination occurs within a few hours following the inoculation of tubercle bacilli into the human body.[2] Therefore, by the time the tuberculin reaction becomes positive all these changes have already taken place in the body. Knowing this, we should appreciate the great clinical significance of a positive tuberculin reaction. Curiously enough, despite such widespread infection, children seldom appear sick with primary tuberculosis; however, this outward appearance of well being should not lull us into the illusion that primary tuberculosis is an innocent disease, because all too frequently more trouble is to come.[3-6] The risk of primary tuberculosis is shown in Figure 1.

Until very recently no effective therapy was known for the treatment

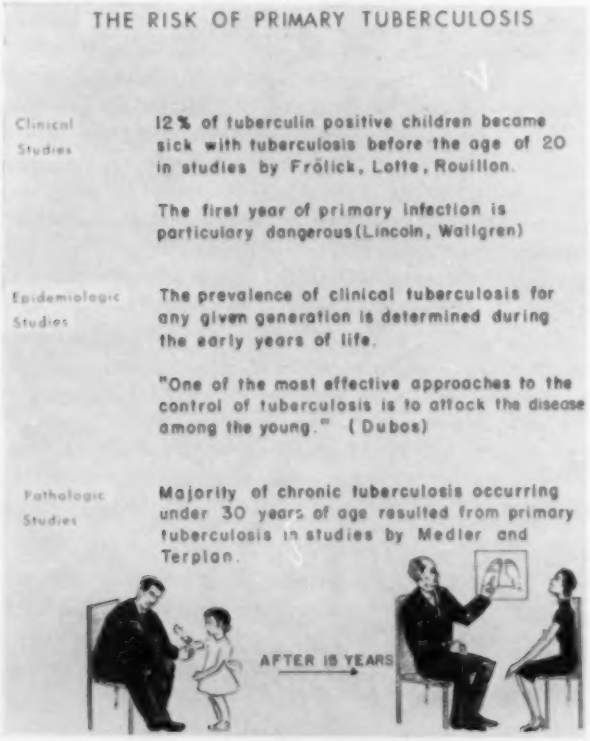


FIGURE 1

of primary tuberculosis. Whether the infection would remain dormant or develop into manifest disease was entirely unpredictable. The discovery of isoniazid has opened a new era. Extensive clinical experience has proved that isoniazid is the most potent and the least toxic of the antituberculosis drugs. Since its general introduction into medicine five years ago, there has been a sharp decline in the incidence of tuberculous meningitis and miliary tuberculosis in children.[7] Figure 2 gives the rationale of isoniazid treatment of primary tuberculosis.[8-10]

This does not mean that every child with primary tuberculosis, as evidenced by a positive tuberculin reaction, should be given isoniazid. Only those with primary tuberculosis in its active stage and whose bodies harbor active tuberculous lesions are likely to profit from the treatment. The detection of active primary tuberculosis requires a careful clinical examination, which has been discussed in another paper.[11] The patients who are considered to have active primary tuberculosis and in whom isoniazid therapy is recommended at the Houston Children's Tuberculosis Clinic are described in Figure 3. With the development of effective agents for the

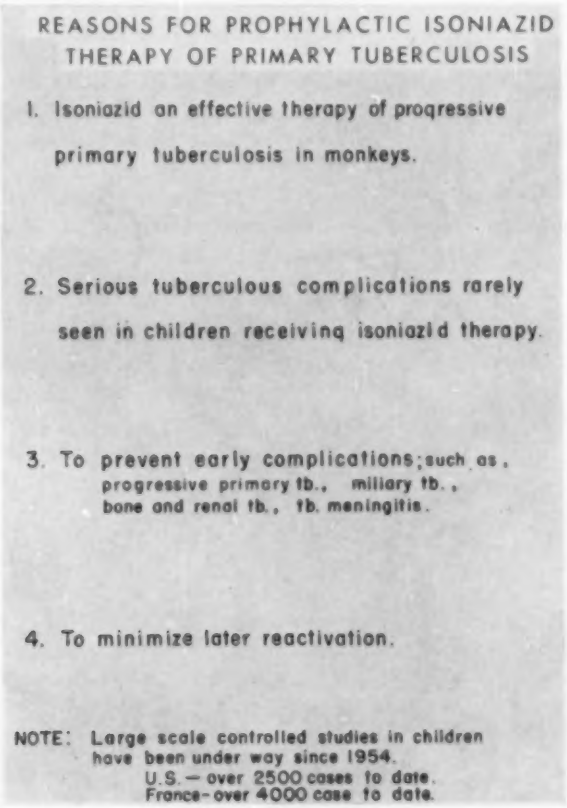


FIGURE 2

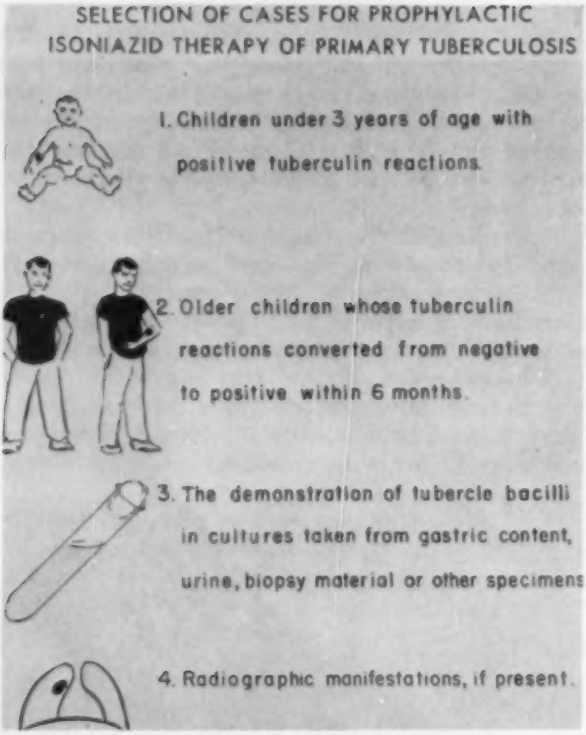


FIGURE 3

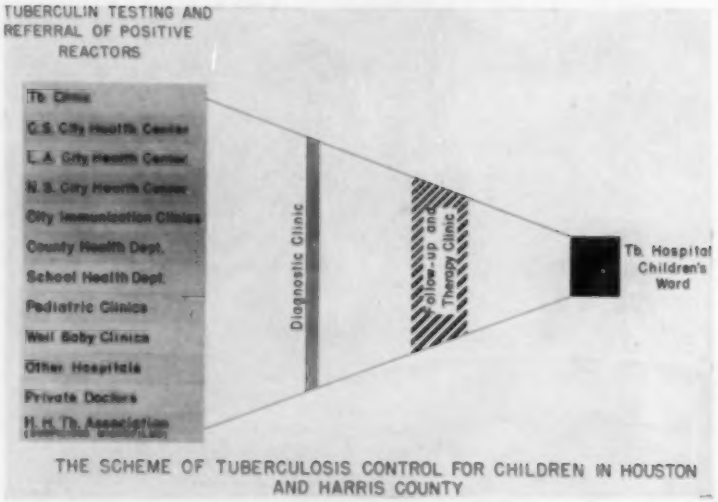


FIGURE 4

treatment of tuberculosis, a diligent search for primary tuberculosis becomes mandatory. Tuberculin testing is the most reliable method of detecting primary tuberculosis. It must be made a routine procedure in well baby clinics, nurseries, schools and children's clinics. In particular, special efforts for tuberculin testing should be directed to infants and adolescents, because primary tuberculosis acquired during these periods of life is liable to develop into progressive disease. The scheme of tuberculosis case finding in children by tuberculin testing in Houston and Harris County is shown in Figure 4.

Fifty years ago the main concern of tuberculosis control was the care of the sick and dying, because the disease could not be diagnosed until a person developed symptoms of consumption. Later, with the introduction of roentgenographic examination it was found that pulmonary tuberculosis could be detected long before a person felt sick. In the past three decades, therefore, much effort has been directed to the finding of tuberculosis by roentgenographic chest surveys. Now we are entering a new era of finding tuberculosis and treating it before roentgenographically demonstrable changes appear. Tuberculin testing has become of paramount importance today, because it is the only reliable test for tuberculosis before the roentgenographic shadow appears. As Dr. Meyers stated in one of his recent articles, "In the past, little effort has been made to attack the vast army of tubercle bacilli to prevent their destructiveness. Most work has consisted of following far behind these armies and trying to repair the damage they have done. The time has arrived when the major attack must be made upon the tubercle bacillus itself rather than waiting until infected persons have developed complications which have resulted in symptoms and liberating tubercle bacilli or casting visible roentgenographic shadows."[12]

Early Diagnosis of Tuberculosis and Prevention of Infection by an Improved Case Finding Technique

Finding tuberculosis is the most important part of tuberculosis control, because unless the cases are found, all the great progress made in treatment will be of no benefit to the patients. Where can tuberculosis be found? Today, in the United States, tuberculosis exists in small nests. Because of the spotty distribution of cases and the lowering of incidence of tuberculosis in the general population, mass x-ray survey has become less and less efficient for tuberculosis case finding. A new method of case finding is in demand if the present epidemiologic situation is to be effectively met. Being a pediatrician, I see the problem from the child's side. Children are sensitive "Geiger counters" of tuberculosis. A positive tuberculin reaction in an infant invariably points to a contagious case of tuberculosis in its immediate environment. In older children recently acquired tuberculin sensitivity has the same significance. Since tuberculosis is transmitted by close contact, examination of the adult and children contacts of these infected children will uncover the nest from which tuberculosis is being spread. We feel this is the most direct approach to the problem of tuberculosis case finding today.

During the past three years a technique of case finding by family contact investigation has been developed in our clinic, the effectiveness of which is illustrated in Figures 6 and 7. Figure 5 is a key to the status of patients shown in all the family contact studies (Figures 6-13). These examples emphasize certain important points concerning family contact investigation:

1. Examination should include not only the immediate family, but also related families which are in frequent contact. A patient with contagious tuberculosis will infect not only his immediate family, but also friends and relatives who have been in close contact with him. It is often necessary to search beyond the immediate household for the source of infection. Once the source is found all contacts must be examined. *This should include both adults and children, because in such family groups more cases of active tuberculosis are found in children than in adults.*
2. Contacts should be examined not once, but periodically. Individuals who have been exposed to tuberculosis may not show signs of tuberculosis on the initial examination; however, if they are observed over

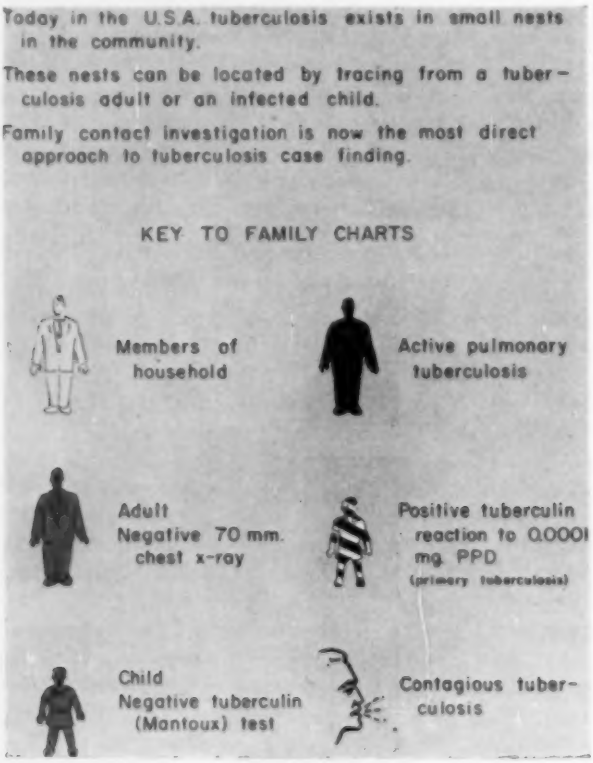


FIGURE 5

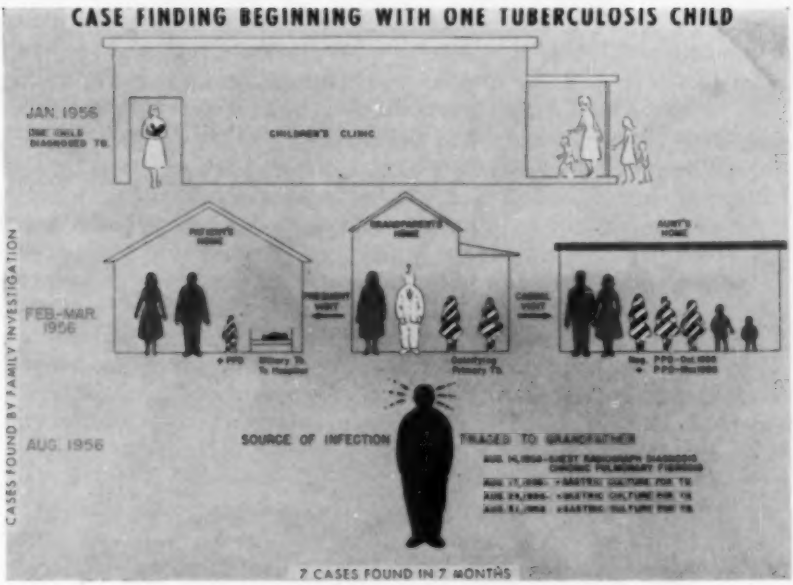


FIGURE 6

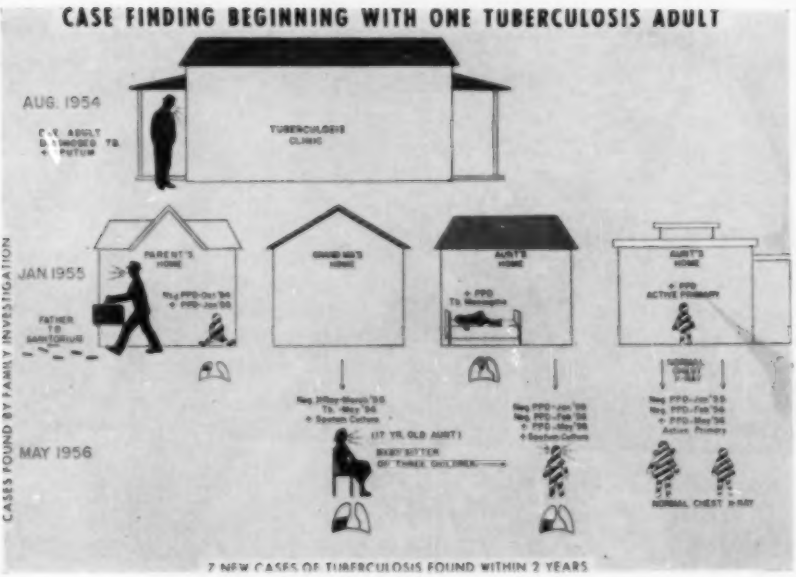


FIGURE 7

a period of time one may see tuberculosis sprout and bloom among them. Children with negative tuberculin reactions may become tuberculin positive in a few weeks or a few months (Figure 7). Adults with initial "negative" chest roentgenographs may develop active tuberculosis on follow up examinations (Figure 7). Watch for sprouts where the seeds have fallen. This is the most fruitful way of finding tuberculosis and finding it early.

3. Injudicious use of tuberculin testing and x-ray examination should be avoided. Children, as well as adults, should be tuberculin tested. There is little reason for substituting roentgenographic examination for tuberculin testing as has been so widely practiced. Today in the United States with children and young adults 70 and 90 per cent tuberculin negative, tuberculin testing has become the most important guide for tuberculosis case finding. Negative tuberculin reactors do not have tuberculosis. What they need is not a chest roentgenograph, but periodic tuberculin skin testing to detect the onset of tubercu-

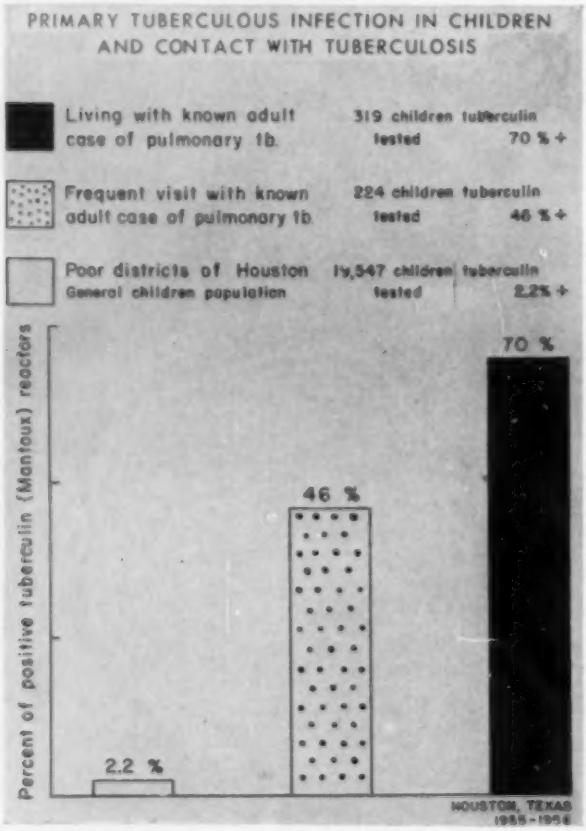


FIGURE 8

lous infection. Positive tuberculin reactors already have the tuberculous infection in their bodies. For this particular group of individuals all facilities and efforts of roentgenographic follow up should be concentrated, because it is from the positive tuberculin reactors that all cases of active tuberculosis evolve.

I have mentioned earlier that the mass x-ray survey is becoming less and less efficient for tuberculosis case finding. This is true the country over and we also find it true in Houston and Harris County. In 1955 the yield of cases of active tuberculosis by mass x-ray survey was only 0.09 per cent, which means that for every 1,000 persons examined in the general population not quite 1 case of active tuberculosis was found. On the other hand, what was found by family contact investigation was quite amazing. At the Houston Children's Tuberculosis Clinic when a child is found to have active primary tuberculosis a family investigation is carried out. Recently, 50 randomly picked family charts were reviewed. It was found that the yield of cases of active tuberculosis in these tuberculous households was as high as 25 per cent of the children and adults examined. This is in sharp contrast to the 0.09 per cent by mass x-ray survey. Many children with active primary tuberculosis do not show roentgenographic shadow. To pronounce a child nontuberculous on the basis of a "negative chest film" is not justified. Indeed, by conferring a false sense of security much harm can be done.

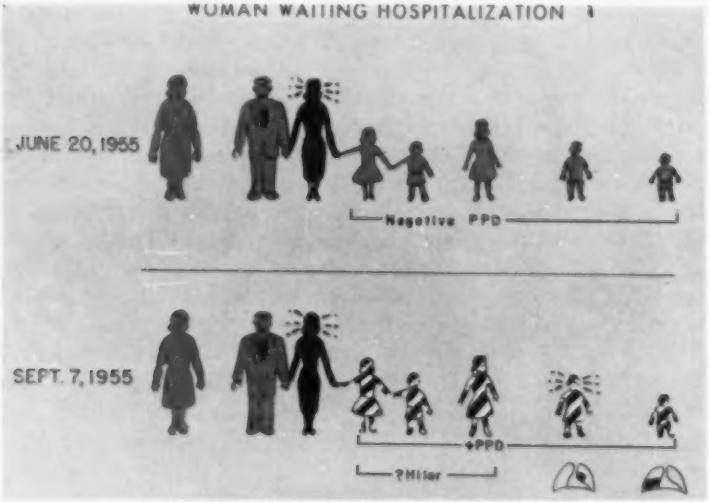
I do not mean to minimize the importance of mass survey. Tuberculin survey and x-ray survey are like the use of radar in navigation. They spot where the dangers lie. Once a danger spot is located, whether it be a tuberculous adult or a tuberculin positive child, it calls for an intensive search for tuberculosis around that case. That is when the real task of case finding begins. Failure to follow through a mass survey by contact investigation is missing the best chance of finding tuberculosis and leaving the most important part of case finding undone. Recently, questions have often been raised as to whether mass x-ray survey is worth the effort in time and money to find so few cases of tuberculosis. I believe it is worthwhile to find these few cases *provided* the few cases found are taken as a clue to locate the nests from which tuberculosis is being spread.

The Importance of Periodic Tuberculin Testing

Primary tuberculosis can be detected in its very early stage by periodic tuberculin testing. Figure 8 indicates that children in contact with tuberculosis run a tremendously higher risk of acquiring tuberculosis than children in the general population. Figure 9 shows five children in one household who became infected within three months from one tuberculous adult. Figure 10 shows how three children converted their tuberculin reactions one after another because the contact with a tuberculous father could not be broken. Even after a child has been removed from a tuberculous home it is important to do retesting. Figures 11 and 12 show how children develop tuberculin sensitivity several weeks after removal from tuberculous environment. Children living with adults who have arrested

tuberculosis may become infected when the disease in the adult reactivates. Figure 13 is an example of the conversion of tuberculin reaction in two children coinciding with reactivation of tuberculosis in the father.

These cases illustrate the contagiousness of tuberculosis and the susceptibility of children to tuberculosis. In these days where there is so much talk about home care of tuberculous patients, it behooves us to think



FIVE CHILDREN INFECTED IN 3 MONTHS

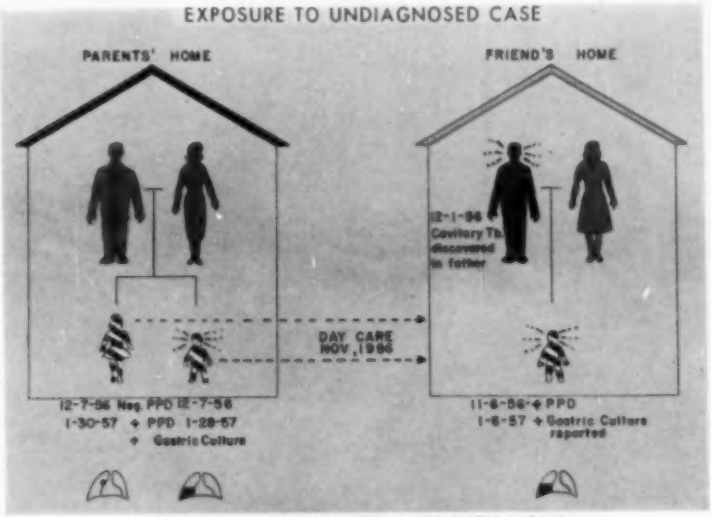
FIGURE 9

3 CHILDREN INFECTED IN 9 MONTHS

FIGURE 10

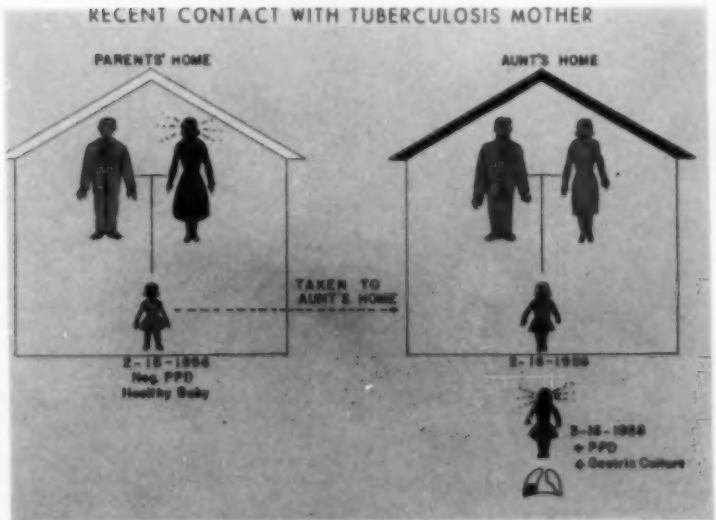
twice before we sacrifice the health of the children in the family for the convenience of adult tuberculous patients. Personally, I feel there is no room for home care of contagious or potentially contagious cases of tuberculosis.

Recent tuberculin converters have primary tuberculosis in its active stage, which we believe will profit by isoniazid therapy. A diligent search



TWO CHILDREN INFECTED IN FRIEND'S HOME

FIGURE 11



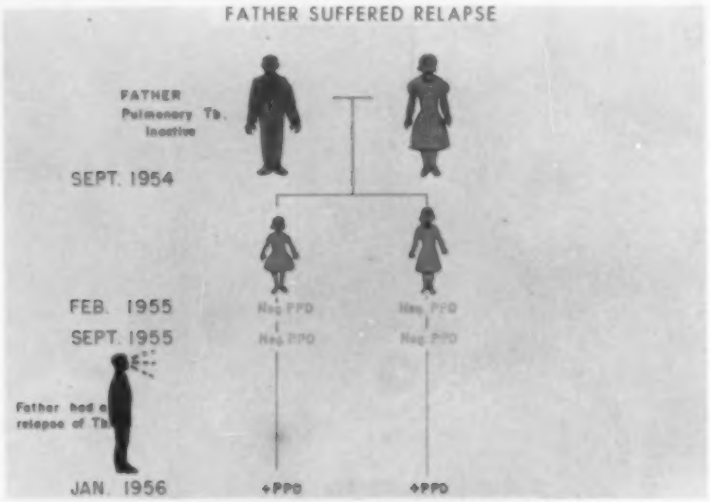
TUBERCULIN BECAME POSITIVE ONE MONTH AFTER SEPARATION FROM MOTHER

FIGURE 12

for fresh primary tuberculosis among the contacts will contribute much to our knowledge of primary tuberculosis and its drug therapy.

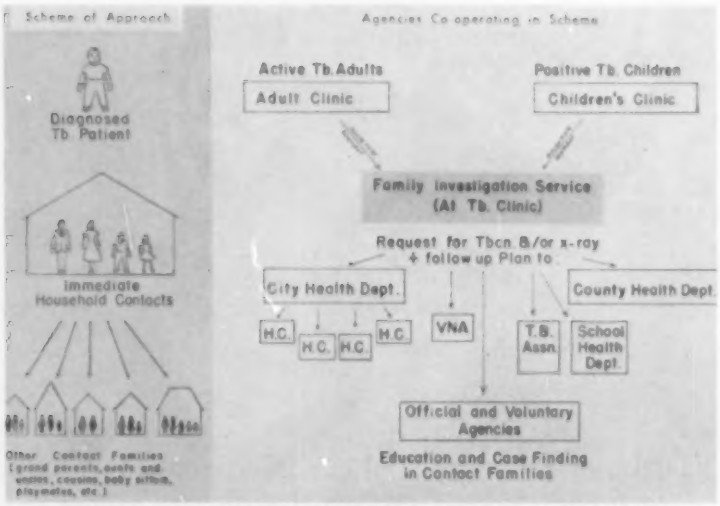
The Need for Organized Effort and Education

Tuberculosis control is a community project. It requires an organized effort of the official and voluntary health agencies as well as the active participation of the public. The easy-going way of reporting tuberculosis cases



TWO CHILDREN BECAME TUBERCULIN POSITIVE

FIGURE 13



PROPOSED SCHEME FOR TUBERCULOSIS CONTACT INVESTIGATION

FIGURE 14

by form letters and paying little or no attention to the contact examination will never control tuberculosis. The initial reporting of the case to the health authorities should include at least the patient and his immediate family. Then the contact families should be identified and examined. The scheme of approach of tuberculosis case finding in Houston and Harris County is shown in Figure 14.

It must be remembered that tuberculosis is largely a hidden infection and a hidden disease. People must be educated to see the hidden danger. Parent education is, therefore, very essential to the success of contact investigation. For without the understanding of the parents, it is impossible to get their cooperation to carry out a thorough contact investigation. At the Houston Children's Tuberculosis Clinic before the clinic starts, a simple talk on the basic facts concerning tuberculosis is given to the parents as a group in the waiting room. After the children have seen the doctor the parents are interviewed individually by a qualified public health nurse. Pictures are used to illustrate the spread of tuberculosis in families and the importance of having every member examined. The significance of the tuberculin test and x-ray examination is explained. Active participation for family contact examination can be expected only after the families have been educated.

SUMMARY

1. We are in a new era of tuberculosis control, a period in which tuberculin testing is assuming a new significance. Because so few children are tuberculin positive today a positive reactor stands out as a warning signal indicating where tuberculosis is being spread and thus pinpointing the spot where intensive search for tuberculosis should be directed.

2. The advent of isoniazid has introduced a new approach to tuberculosis control; that is, prevention of tuberculous sickness by early drug therapy of primary tuberculosis. This calls for intensive tuberculin testing programs to seek out infected children in order to afford them the protection of modern drug therapy.

3. Family contact investigation is the most effective method of finding tuberculosis today. It must be carried out with every new case of tuberculosis found, whether it be a tuberculous adult or a tuberculin positive child.

4. For a thorough and systematic contact investigation the organized effort of health agencies and education of the public are essential.

Acknowledgment: The family contact investigations were coordinated at the Children's Tuberculosis Clinic by Lena E. Pecover, R.N., a staff member of the Houston Harris County Tuberculosis Association. The investigation was carried out with the able cooperation of the nursing departments of Houston City Health Department and of Harris County Health Department.

RESUMEN

1. Nos encontramos en una era nueva del control de la Tuberculosis en la que las reacciones tuberculínicas asumen una significación nueva. En virtud de que tan pocos niños son tuberculino-positivos ahora, un reactor positivo se destaca como una señal de advertencia que señala donde está desarrollándose una diseminación de la tuberculosis y apuntando así al lugar donde debe hacerse una investigación rigurosa.

2. El advenimiento de la isoniacida ha introducido una nueva manera de atacar el problema del control de la tuberculosis; tal es la prevención de la enfermedad tuberculosa por el tratamiento temprano de tuberculosis primaria. Esto requiere planes intensos de búsqueda de niños infectados por medio de la reacción tuberculínica para ofrecerles la protección de la drogoterapia moderna.

3. La investigación del contacto familiar es el método más efectivo de encontrar la tuberculosis al presente. Debe investigar se en cada caso nuevo encontrado ya se trate de un adulto o de un niño tuberculino-positivo.

4. Para la investigación sistemática de los contactos el esfuerzo organizado de las unidades de salubridad y de educación del público, se consideran esenciales.

RESUME

1. Nous sommes dans une nouvelle phase de l'éradication de la tuberculose, une phase dans laquelle le test à la tuberculine prend une valeur nouvelle. Parce qu'il y a maintenant peu d'enfants qui réagissent à la tuberculine, le porteur de réactions positives se dresse comme un signal d'alarme pour indiquer le foyer de la tuberculose, et les lieux où doivent être intensifiées les recherches.

2. L'apparition de l'isoniazide a introduit un nouveau moyen qui laisse espérer la disparition de la tuberculose; c'est la prophylaxie de la maladie tuberculeuse par l'administration précoce de la médication lors de la primo-infection. Ceci demande un programme intensif de tests à la tuberculine, pour découvrir les enfants infectés, afin de leur apporter la protection des médications modernes.

3. Les investigations portant sur les contaminations familiales sont le moyen le plus efficace pour découvrir la tuberculose aujourd'hui. Elles doivent être mises en oeuvre pour chaque nouveau cas de tuberculose, que ce soit un adulte tuberculeux ou un enfant porteur de réactions positives.

4. Il est capital de coordonner l'effort des services de santé publics et l'éducation du public pour aboutir à un contrôle complet et systématique.

ZUSAMMENFASSUNG

1. Wir befinden uns jetzt in einer neuen Aera der Tuberkulose-bekämpfung, einer Periode, in der die Tuberkulinprüfung eine neue Bedeutung gewinnt. In Anbetracht dessen, dass heute so wenig Kinder tuberkulin-positiv reagieren, tritt eine Person mit positiver Reaktion in den Vordergrund als ein Warnungszeichen, das darauf hinweist, von wo sich die Tuberkulose auszubreiten im Begriffe steht, und das auf diese Weise den Punkt markiert, an dem intensive Tuberkulosebekämpfungsmassnahmen angesetzt werden müssen.

2. Die Einführung des INH hat einen neuen Weg für die Tuberkulose-bekämpfung eröffnet; nämlich die Verhinderung der Tuberkulose als Krankheit durch frühzeitige medikamentöse Therapie der Primärtuberkulose. Dieser Umstand spricht zu Gunsten eines intensiven Tuberkulin-

prüfungsplanes zur Auffindung infizierter Kinder mit dem Ziel, diesen einen Schutz in Form der modernen medikamentösen Therapie zu gewähren.

3. Untersuchungen von intrafamiliären Kontaktfällen sind die bestwirksame Methode, um heute eine Tuberkulose zu entdecken. Sie müssen bei jedem neugefindenen Tuberkulosefall ausgeführt werden, sei es nun ein tuberkulöser Erwachsener oder ein tuberkulinpositives Kind.

4. Um eine durchgehende und systematische Kontaktuntersuchung ausführen zu können, bedarf es der geplanten Bemühungen der Gesundheitsbehörden und einer Erziehung der Öffentlichkeit.

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Radiopaque Grass Heads in the Lung

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Two patients have recently presented themselves with a radiological diagnosis of "calcified grass head" in the right lower lobe of the lung. Their clinical course was almost identical, and after surgical removal of the panicles both did well.

The radiological features of this disease have not been previously reported. The diagnostic and therapeutic aspects have been radically altered by developments during the past decade.

Case 1: In September, 1952 an 18 year old student (SH 57482) was found on routine photofluorogram (Figure 1) in the Student Health Service to have an obliterated right costophrenic sulcus. On a recheck 14 x 17 roentgenogram a calcified foreign body similar in shape to a grass head was observed in the right lower lung field. Although he was asymptomatic he recalled that in 1942, he choked on a piece of grass held in his mouth while talking. He denied subsequent illness at that time.

In the summer of 1945, he recalled picking wild berries in the country. This was followed by an acute gastric upset with chills, fever, nausea and vomiting. He did not recall choking at this time. Pneumonia was diagnosed and treated with penicillin. Two weeks later, after partial recovery, he had an hemoptysis of about one-half ounce. Lung abscess was diagnosed by x-ray film. Bronchoscopy was not done. Fever and pain gradually subsided without further penicillin therapy.

Subsequently, he has been completely asymptomatic. Between September 1952 and June 1955 this lesion was followed by serial chest x-ray films. He did not want other studies done.

In the summer of 1955, 13 years after his episode of choking and 10 years after his "lung abscess," he was on maneuvers with his Reserve Officer's Training Corps unit when he developed an upper respiratory infection followed by hemoptysis. This infection lasted about three weeks and left him with a cough. A few weeks later he coughed up a hard piece of material, which he thought was a segment of the foreign body. An x-ray film taken at this time showed that part of the panicle had indeed disappeared and there was considerable infiltration around the remaining segment.

Bronchograms (Figure 2) then revealed bronchiectasis of the posterior basal segment of the right lower lobe. Bronchoscopy showed purulent drainage from all right basal segments. Thoracotomy revealed a large sacular bronchiectatic abscess cavity which extended to the pleural space. Since the orifices to all basal segments were involved, the entire right lower lobe was removed. The pathological process in the resected lobe included generalized bronchiectasis throughout the lower lobe bronchi with abscess formation localized to the posterior basal and medial basal segments. The subsequent course has been uneventful but characterized by rapid weight gain.

Case 2: A 25 year old white man, (Number B8274), was admitted from the Veterans Administration Outpatient Clinic with a complaint of hemoptysis. A calcified panicle in the right lower lobe was diagnosed on the admission chest x-ray film (Figure 3).

At the age of 11 he had aspirated a "piece of foxtail grass" which was followed by "double pneumonia" and "lung abscess." Hemoptysis occurred during the initial illness, and again at 17 and at 21 years of age. At the age of 24 he had chronic cough with approximately 30 cc. of yellow sputum per day. Persistent hemoptysis and weight loss developed. Bronchograms (Figure 4) revealed extensive right lower lobe bronchiectasis and confirmed the presence of the calcified grass head in the posterior basal segment. Thoracotomy was performed which revealed obliteration of the right pleural space and basilar bronchiectasis. Segmental resection was performed. The excised lung contained a panicle which measured 6 cm. in length. The bronchi were dilated, the pleura was thickened, and the parenchyma was the site of chronic pneumonia. The postoperative course has been uncomplicated.

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Discussion

These two cases are unique in respect to the positive identification of the grass panicle which established the diagnosis prior to surgery.

The course of patients who have aspirated panicles of such grasses has been well documented.[1, 4, 5] These barbed plant structures are unique among foreign bodies in that they rapidly move out of the range of effective endoscopy. Although their forward motion is apparently spontaneous, it is actually the result of the almost constant to-and-fro respiratory motion of the tracheo-bronchial system combined with the backward restraints of the barbed panicle. Together a "one way travel" results.[2] Usually the panicle migrates into the basal segments of the right lower lobe.

Ross[5] collected 14 cases of grass head aspiration from the medical literature in 1954. In his cases the grass head worked its way through the trachea, bronchi, lungs, pleura and extruded spontaneously through the chest wall and skin. A strikingly similar series of events is described in the isolated case reports of Seydall,[7] Purcell,[3] Schring and Shaw[6] and others. Recently, instances of surgical resection of bronchiectatic segments or of lung abscesses have been followed by the discovery of a grass head within the removed specimen. Earlier reports contain many examples of grass heads found at autopsy following death from pulmonary infection. Radiologic diagnosis of grass head in the lung has never been previously reported, so far as can be determined. It seems that in the pre-antibiotic era the usual course following aspiration of such a grass panicle

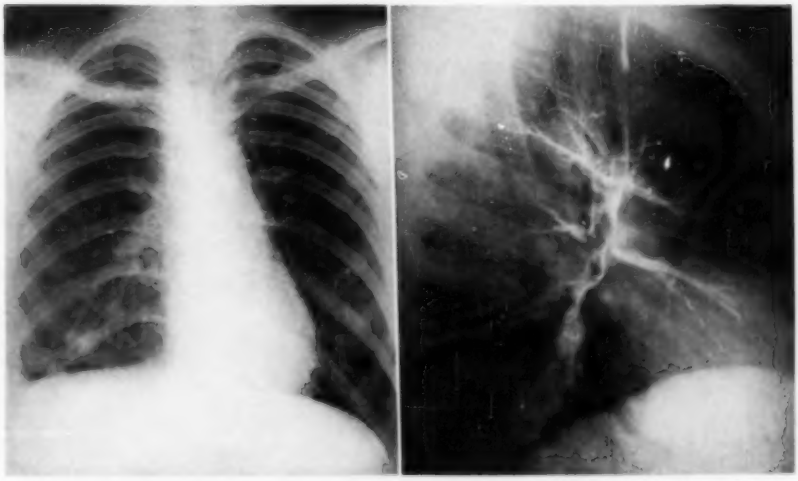

FIGURE 1 FIGURE 2

Figure 1 (Case 1): Calcified grass head in right lower lung noted first on routine photofluorogram because of pleural reaction at right base.—*Figure 2* (Case 1): Bronchiectatic basilar segments surround the calcified panicle. The upper and middle lobes and the apical segments of the lower are not involved.

was either (a) rapid passage of the foreign body through the thoracic wall with an accompanying acute febrille illness, or (b) death due to acute or subacute pulmonary infection.

In these two cases antibiotic therapy undoubtedly enabled these patients to tolerate the initial acute infection produced by the foreign body. In Case 1, a suppurative tract which extended to the pleural space was formed, the pleural space was obliterated, but there progression ceased. In both cases a state of tolerance to the foreign body developed and continued for a decade with encrustation of the vegetable matter by calcium salts. The end product was a cast of the original "grass head" in calcium which was identified on a routine recheck of a chest photofluorogram (Case 1) and on a hospital admission chest x-ray film (Case 2). In both patients extensive bronchiectasis was produced with symptoms characteristic of this condition eventually becoming manifest. Hemoptysis brought both patients to the hospital where the offending panicle was found in the posterior basal segment of the right lower lobe.

SUMMARY

The course followed by patients who aspirate panicles of certain grasses, known as "grass heads" is characterized by either (a) spontaneous passage through the lung and thoracic cage to the exterior or (b) the formation of chronic lung abscess and/or bronchiectasis.

These are usually in the right lower lobe. In the two cases described it was possible to make a preoperative radiologic diagnosis of retained "grass head" in the lung more than a decade after the aspiration occurred.

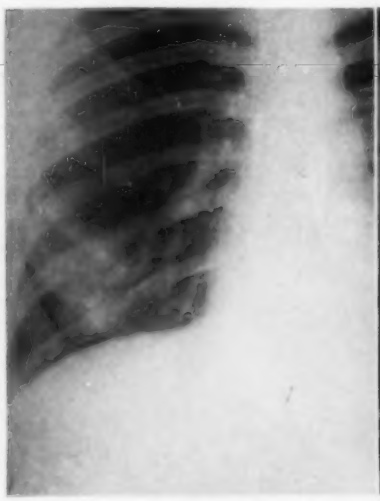

FIGURE 3

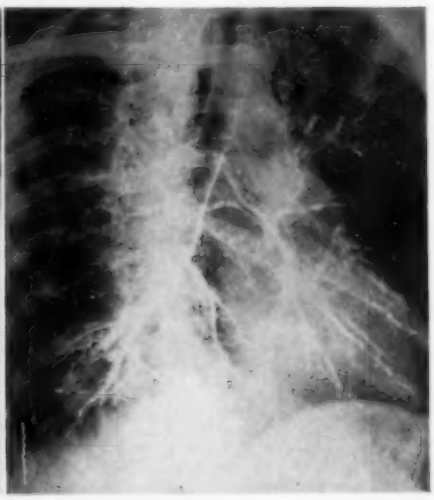

FIGURE 4

Figure 3 (Case 2): Calcified panicle in posterior basal segment of the right lower lobe noted on hospital admission chest roentgenogram.—*Figure 4* (Case 2): Bronchiectatic posterior basal segment of right lower lobe surrounding the calcified grass head. This patient was admitted because of hemoptysis.

Both cases were successfully treated by resection of the foreign body together with the bronchiectatic pulmonary segments.

Routine photofluorograms showing evidence of basal pleuritis, particularly on the right side, should be studied for the possibility of retained foreign body.

RESUMEN

La evolución de los enfermos que aspiran panículos de ciertas grasas, conocidas como "cabezas de grasa" (grass heads) se caracteriza por (a) ya sea el paso espontáneo a través del pulmón y la caja torácica hacia el exterior o (b) la formación de abscesos pulmonares crónicos y/o bronquiectasia.

Estos están habitualmente en el lóbulo inferior derecho. En los dos casos descritos fuó posible hacer un diagnóstico radiológico preoperatorio de "grass head" retenida en el pulmón más de una década después de que ocurrió la aspiración.

Ambos casos fueron tratados con buen resultado por la resección del cuerpo extraño junto con los segmentos pulmonares bronquiectásicos.

Los fotofluorogramas de rutina mostrando evidencias de pleuritis basal, particularmente en el lado derecho, deben ser estudiados ante la posiblidad de que se trate de retención de cuerpos extraños.

RESUME

L'évolution que suivent les épis de certaines herbes inhalés est caractérisée par: a) soit le cheminement spontané à travers le poumon et la cage thoracique vers l'extérieur b) soit la formation d'abcès chroniques du poumon accompagnés ou non de bronchectasie.

Ils sont généralement situés dans le lobe inférieur droit. Dans les deux cas décrits, il était possible de faire un diagnostic radiologique préopératoire de rétention intrapulmonaire d'épis d'herbe plus d'une décade après l'aspiration.

Les deux cas furent traités avec succès par exérèse du corps étranger, et des segments pulmonaires bronchectasiés.

Les radioscopies systématiques, montrant une atteinte pleurale de la base, particulièrement du côté droit, doivent être considérées en gardant présente à l'esprit la possibilité d'un corps étranger.

ZUSAMMENFASSUNG

Der Krankheitsverlauf, den Patienten nehmen, die Rispen von bestimmten Gräsern aspirieren, die unter dem Namen "Grasköpfe" bekannt sind, ist gekennzeichnet, entweder a) durch eine spontane Passage durch die Lunge und Thoraxwand nach aussen oder b) durch die Bildung eines chronischen Lungenabszesses und/oder Bronchiektasie.

Diese liegen gewöhnlich im recten Mittellappen. Bei den 2 beschriebenen Fällen war es möglich, vor der Operation die radiologische Diagnose zurückgebliebener "Grasköpfe" in der Lunge zu stellen, und zwar mehr als 10 Jahre, nachdem sich die Aspiration ereignet hatte.

Beide Fälle wurden erfolgreich behandelt mittels Resektion des Fremdkörpers zusammen mit den bronchiektatischen Lungensegmenten.

Übliche Schirmbildaufnahmen, die Anhaltspunkte für eine basale Pleuritis aufweisen, besonders auf der rechten Seite, sollte man prüfen auf die Möglichkeit von zurückgebliebenen Fremdkörpern.

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Hamartoma of the Lung

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Hamartoma of the lung is infrequently suspected on routine x-ray film examination or found at autopsy. Its appearance on the roentgen film frequently simulates that of malignant neoplasm although the tumor itself rarely, if ever, becomes malignant. We have reviewed the hamartomas of the lung which were discovered both in surgical pathologic material and at autopsy in order to determine the incidence of the tumor, characteristic diagnostic features, and the association of any factor that might throw light on etiology and pathogenesis.

The term hamartoma is defined as a tumor-like malformation in which can be found an abnormal mixture of normal developmental components of the organ in which they occur. The mixture may be abnormal with regard to quantity, arrangement, degree of development, or all of these factors.

General Features

Incidence: McDonald and associates[1] reported 20 hamartomas of the lung in 7,972 autopsies at the Mayo Clinic, an incidence of 0.25 per cent. Novi[2] stated that less than 200 cases have been reported in the world literature. During the past six years approximately 60 cases have been reported.[1-10] Thomas[12] found 10 hamartomas among 459 primary lung tumors; in his series, hamartomas constituted 17 per cent of the benign tumors. Hood and associates[11] of the Mayo Clinic found that 16 per cent of "coin" lesions of the lung were hamartomas. The increased incidence of hamartomas in recent years is undoubtedly a reflection of the more frequent routine x-ray film examination of the chest and of the increased number of thoracotomies for resection of "coin" lesions that have been found in the lung.

Location: In the 200 reported cases, the tumor was endobronchial in 33 and in the lung parenchyma in the remainder. It occurs more frequently in the lower lobes, is usually found immediately beneath the pleura, but may lie deep in the parenchyma near the larger bronchi and blood vessels.

Size: The tumor may reach 20 cm. but most of those reported in recent years have ranged from 1 to 4 cm. in diameter.

Shape and color: Hamartomas are usually spherical or ovoid, are loosely encapsulated and can be easily shelled out of the adjacent parenchyma, and have a firm, rough, bosselated surface. They cut with the consistency of cartilage and may contain small areas of calcification. The cut surface is usually gray-white, although tumors having an abundance of fat may be yellow.

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Composition: Cartilage is the predominant tissue and may be of hyaline, fibrous or elastic type. The lobules of cartilage are separated by a loose, sometimes myxomatous, connective tissue which is associated with clefts and cystic spaces lined by cuboidal or columnar cells. Smooth muscle fibers are frequently seen and fat is almost invariably present, both at the periphery and occasionally in the center of the tumor. Hamartomas are also sometimes classified as mixed tumors and almost all cartilage-containing tumors of the lung are hamartomas. Two pure chondromas of the lung have been reported.

Complications: Zeithofer[4] reported a hamartoma with carcinomatous change, invasion of bronchial wall and metastasis to hilar lymph nodes. This is of rare occurrence, and may represent concomitant carcinoma of bronchial epithelium not at all associated with the primary hamartoma. Several cases have been described of carcinoma in the same or opposite lung as the hamartoma. When carcinoma of the lung is associated with hamartoma of the lung, the hamartoma may be erroneously interpreted in the roentgenogram as a metastatic growth of the carcinoma.

Bronchoscopic Appearance: According to Sherrick,[5] endobronchial hamartomas have a smooth, yellow or gray-yellow external surface and are often polypoid or pedunculated.

Roentgen Characteristics: Most hamartomas are unattended by symptoms and are discovered in routine x-ray films of the chest, appearing as a

TABLE I
GROSS CHARACTERISTICS OF NINE HAMARTOMAS OF THE LUNG

Number	Age	Sex	X-Ray Film Visualization	Site*	Location	Diameter In Cm.	Associated Pulmonary Disease	Color and Consistency
1	76	F	No	RLL	Parenchymal	2.6	Lobar pneumonia	Yellow-white, firm
2	76	F	No	LL**	Subpleural	....	Bronchopneumonia, metastatic carcinoma	Pink-gray, firm
3	76	M	No	LLL	Subpleural	1.5	Organizing bronchopneumonia	Yellow, soft
4	56	F	No	RLL	Subpleural	4	Pulmonary infarcts, bronchiectasis	Yellow, firm
5	93	M	No	LUL	Subpleural	3	Bronchopneumonia, bronchiectasis, chronic pneumonitis	White, firm
6	85	F	No	LLL	Subpleural	2	Atelectasis, fibrosis	White, firm
7	68	F	Yes	RUL	Subpleural	3	Purulent bronchitis, bronchopneumonia	Gray-white, firm
8	52	M	Yes	LLL+	Subpleural	1		White, firm
9	59	F	Yes	LUL+	Subpleural	1.5		Gray, firm rubbery

*RLL indicates right lower lobe; LLL, left lower lobe; etc.
**Location in lung was not recorded.
+ Tumor was surgically resected.

dense shadow. According to Hall,[15] the appearance of small calcifications scattered through a discrete smooth-margined, round or lobulated mass which is surrounded by normal lung tissue is unusual and should at once suggest a hamartoma. Generally, however, the roentgen features are not diagnostic.

Clinical Features in Present Series

In the past 24 years at this hospital, seven hamartomas of the lung have been encountered in 10,107 autopsies, an incidence of 0.069 per cent. Two other hamartomas were surgically excised during the latter part of the same period. The details of the clinical findings and of the gross features are summarized in Table I. Blocks of tissue from the tumor and in some instances the entire tumor were fixed in 10 per cent formalin, embedded in paraffin, sectioned and routinely stained with hematoxylin and eosin, Masson's trichrome stain for connective tissue, van Gieson's stain, Verhoeff's elastica stain and periodic acid-Schiff stain. In one instance (Case IV) only the microscopic sections, stained with hematoxylin and eosin, were available for study. Details of the histologic structure of these tumors are summarized in Table II.

Sex Distribution: In the 20 hamartomas reported by McDonald and his associates[1] the ratio of men to women was 3 to 1, but in our 9 cases the ratio of men to women was 1 to 2.

Age: Although pulmonary hamartomas are found at all ages, most are discovered in older persons at autopsy. In our series the oldest person was 93 years old, the youngest 52 years. In three of our nine patients the tumor was seen on roentgen films of the chest, and in all three cases the lesion was thought to be either a Ghon tubercle or a malignant tumor. In six, failure to visualize the tumors in the roentgen film may be attributed either to its small size or to its obscurement by other pathologic alterations in the lung or pleura.

TABLE II
HISTOLOGIC CHARACTERISTICS OF HAMARTOMAS OF THE LUNG

Histologic Feature	Case Number								
	1	2	3	4	5	6	7	8	9
Cartilage	+	—	—	+	+	+	+	+	+
Hyaline	+	—	—	+	—	+	+	+	—
Elastic	—	—	—	—	+	—	—	—	+
Mesenchymal condensation	+	—	+	+	—	+	+	+	+
Connective tissue	+	+	+	+	+	+	+	+	+
Fat	—	+	+	—	—	+	+	+	+
Smooth muscle	—	—	+	—	—	+	+	+	+
Epithelial cells	+	+	+	+	—	+	+	+	+
Columnar	+	+	+	+	—	+	+	—	—
Cuboidal	+	+	+	+	+	+	+	+	+
Lymphocytic infiltration	+	+	+	+	+	+	+	+	+

+ indicates presence; —, absence.

Gross Pathologic Features

Six hamartomas were located in the right lung and three in the left; five were in the lower lobes, two in the upper, and in one instance (Case 2) the location was not recorded. Eight were found immediately beneath the pleura and one lay deep within the lung parenchyma near the hilum. The maximum diameter ranged from 1 to 4 cm. and the median diameter was 2.6 cm. All the tumors were well circumscribed, most were gray-white, and in two the central portion of the tumor was calcified.

Histopathology

Seven of the tumors contained cartilage; in five the cartilage was hyaline and in two, elastic. The cartilage was bordered by loose, cellular, myxomatous connective tissue which in all cases was PAS-positive. The periphery of the larger nodules frequently contained small satellite nodules of newly formed cartilage as well as condensed areas of myxomatous connective tissue, representing an early stage in cartilage formation. The cartilage was of normal appearance. In one case the hamartoma was composed entirely of elastic cartilage and no epithelial cleft, connective tissue, smooth muscle or fat was observed; this structure was suggestive of the so-called "pure" chondroma of the lung (Fig. 1).

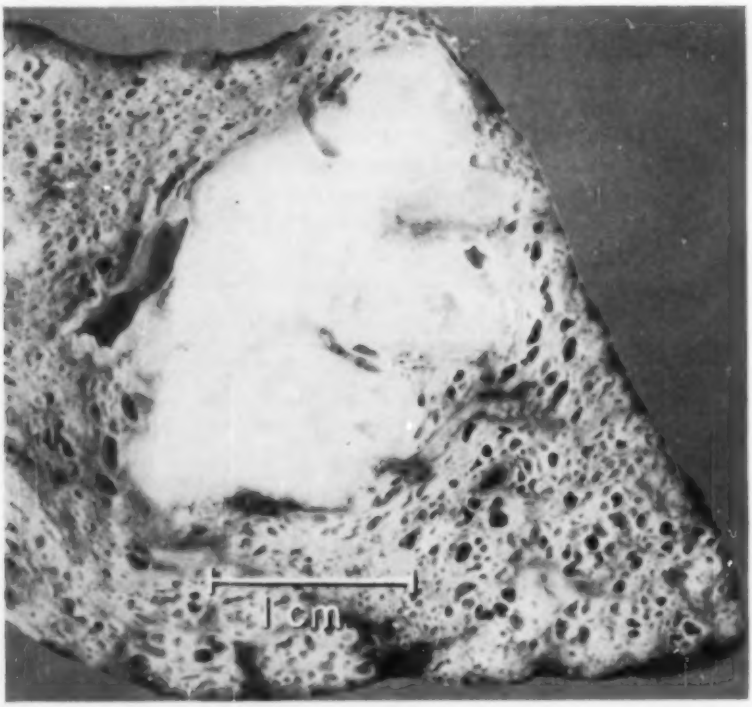

FIGURE 1: Chondroma of lung. The tumor is subpleural and appears to arise in the wall of a bronchus. The surrounding lung is the site of bronchiectasis, severe chronic pneumonitis and fibrosis. (X 2).

Fat: Six of the nine hamartomas contained adipose tissue, usually at the periphery but occasionally in and around small epithelial clefts that extended into the center of the tumor. The adipose tissue was present in the form of small clumps of fat cells but at times individual fat cells were seen in the loose myxomatous connective tissue. In all cases the fat cells were of the adult type.

Connective Tissue: Connective tissue was present in eight tumors and usually was loose and fibrillar. At the periphery dense collagenous fibers frequently formed a pseudo-capsule.

Smooth muscle was found in five instances, appearing as small bundles, and was located in the connective tissues supporting the epithelial clefts.

Epithelial Elements: Small clefts and epithelial-lined cystic spaces were seen in eight cases. Small glands were present beneath the epithelium in several cases; this could represent either true gland formation, or more likely small fragments of epithelium pinched off by the expanding cartilage and connective tissue. The clefts were lined for the most part by cuboidal cells. In several areas, however, there were mucus-secreting, ciliated columnar cells which occasionally showed pseudo-stratification. Most of the epithelium-lined spaces were located at the periphery of the tumor and frequently displayed a polypoid appearance. Occasionally small clefts extended into the center of the tumor, usually along with ingrowths of connective tissue passing between the islands of cartilage (Fig. 2).

Inflammatory cell infiltration was seen in some degree in all cases, usu-

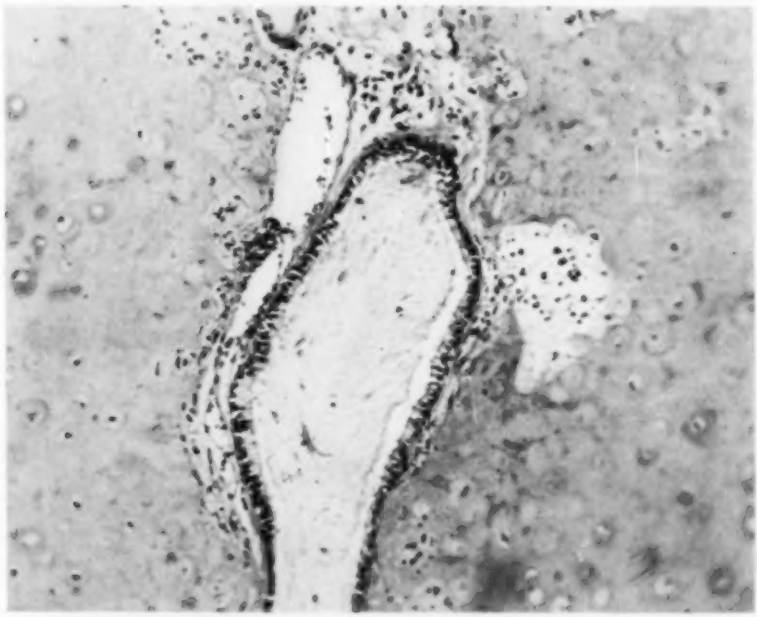

FIGURE 2: Small epithelial cleft of bronchial epithelium enclosed within expanding cartilage. (X 140).

ally mainly at the periphery, in the submucosal connective tissue and in the adjacent lung parenchyma. Most of the cells were lymphocytes, although plasma cells, eosinophils and, more rarely, neutrophilic granulocytes were also present (Fig. 3).

Calcification: In two instances the hyaline cartilage contained focal areas of calcification.

Discussion

The hamartoma usually originated in the wall of the small bronchi or bronchioles in the periphery of the lung and gradually expanded and compressed the adjacent lung parenchyma (Fig. 4). Their appearance suggested growth both into the bronchial lumen as well as into the adjacent lung. In two cases in which the tumors cast x-ray shadows, x-ray films six years previously were negative. In both of them the tumor was later removed because it showed evidence of growth.

Etiology: Four possible mechanisms of origin of hamartomas have been proposed: 1) congenital malformation, 2) hyperplasia of normal structures, 3) neoplasia, and 4) response to inflammation. Most writers feel that these tumors represent a misplaced bronchial anlage. The lungs develop by a process of budding from the primitive bronchi, the most primitive areas being at the periphery. The columnar epitheluim of these primary bronchi is surrounded by membrana propria. The connective tissue framework of the lung gives rise to smooth muscle and cartilage. According to Möller (cited by Carlsen and Kiaer),[7] the tumor is caused by localized abnormality in development of the bronchi; instead of the normal fetal inversion of the terminal tubes of the bronchial tree there may be at one site, inversion of epithelium and mesenchyma. Other writers[6] feel that

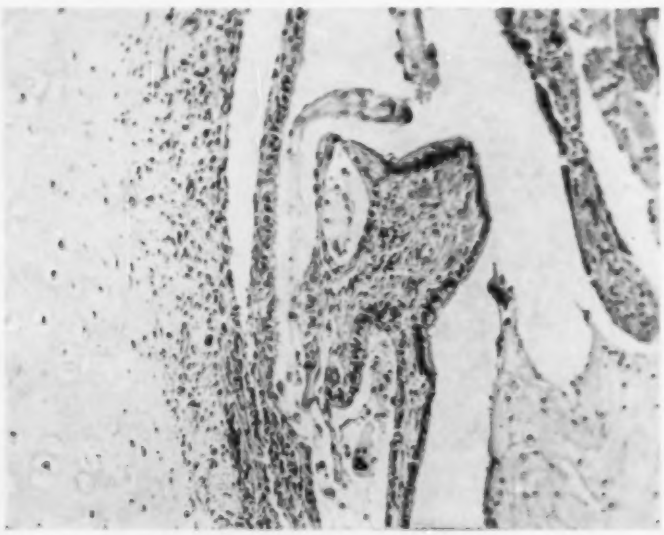

FIGURE 3: Portion of periphery of tumor compressing bronchial epithelium. Note lymphocytic infiltration of subepithelial connective tissue. (X 140).

the tumor arises by proliferation of bronchial epithelium which in its growth mimics development of the bronchi but is directed toward the lumen rather than toward the lung parenchyma. There is no preformed cartilage in the peripheral portion of the lung where most of these tumors arise and it has been adequately demonstrated that in true endobronchial hamartomas, the cartilage of the tumor has no connection with the normal occurring cartilage located in the bronchial wall.[8] Therefore, it appears that the tissues found in the hamartomas arise from connective tissue of the bronchial wall as in fetal development.

In all seven hamartomas found at autopsy, infiltration of lymphocytes, plasma cells and granulocytes were present at the periphery of the tumor and often in the connective tissue which separated the lobules of cartilage. There was also inflammatory reaction in the adjacent pulmonary parenchyma. In most of the lungs chronic inflammation varied from small focal areas of fibrosis associated with lymphocytic infiltration to marked, diffuse, chronic pneumonitis with fibrosis. During resolution of a pneumonic exudate the lung contains an unusually high concentration of fibrinolytic enzyme.[13] The resolution of fibrinous inflammatory exudate and the formation of granulation tissue, according to Selye,[14] is under hormonal control. Since animal experiments indicate that cortisone and corticotropin can prevent fibroplasia, we examined the adrenal glands for evidence of hyperplasia and found that in all cases the adrenal gland showed increase

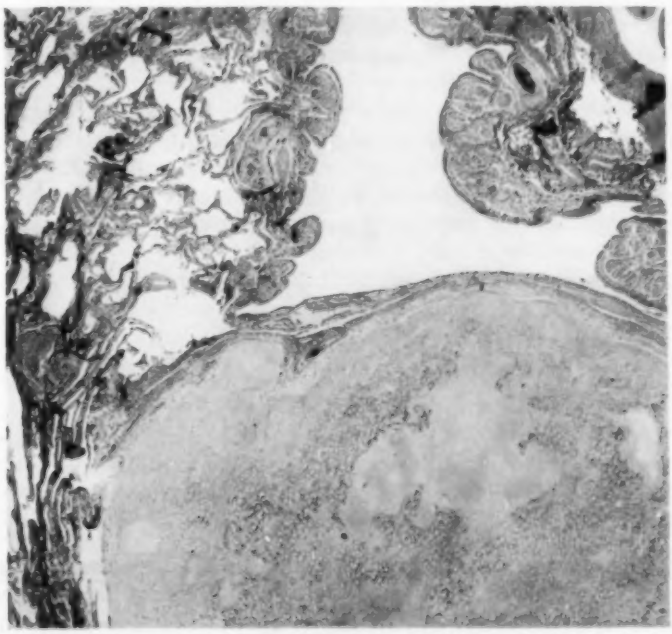

FIGURE 4: Section of the hamartoma arising in the wall of bronchus and extending into its dilated lumen. (X 10).

in the weight of the organ, or increase in thickness of the cortex. Although its significance is not clear, the question may be raised if, in some cases of chronic inflammation of the lung, hyperplasia of the adrenal cortex may not have been responsible for retardation of fibroplasia of the lung.

SUMMARY

Approximately 200 hamartomas of the lung have been reported; 33 of these were of the endobronchial type.

The tumors seldom give rise to symptoms and are usually discovered during routine roentgen examination of the chest. They frequently simulate chronic granuloma or malignant neoplasm on the roentgen film although they rarely if ever become malignant.

Nine new cases are presented, one of which seems to be a "pure" chondroma. The tumors arose from the connective tissue of the bronchial wall and expanded outward into the lung parenchyma as well as inward into the bronchial lumen. All of the hamartomas were associated with an infiltration of chronic inflammatory cells and many were found adjacent to areas of chronic pneumonitis and fibrosis.

The possibility is suggested that chronic inflammation may be a factor, in some cases, in formation of pulmonary hamartoma.

RESUMEN

Se han reportado aproximadamente 200 hamartomas del pulmón; 33 de ellos eran del tipo endobronquial.

Los tumores rara vez dan lugar a síntomas y se descubren habitualmente durante exámenes radiológicos de rutina. Frecuentemente simulan el granuloma crónico o la neoplasia maligna en la radiografía aunque rara vez si acaso se hacen malignos.

Se presentan nueve casos nuevos uno de los cuales parece ser un condroma "puro." Los tejidos nacen del tejido conectivo de la pared bronquial y se expanden hacia afuera dentro del pulmón así como hacia la luz del bronquio. Todos los hamartomas estaban asociados con una infiltración de celdillas inflamatorias crónicas y muchos fueron encontrados adyacentes a áreas de neumonitis crónica y fibrosis.

Se sugiere la posibilidad de que la inflamación crónica sea un factor en algunos casos para la formación del hamartoma pulmonar.

RESUME

Environ 200 cas d'hamartomes pulmonaires ont été rapportés. 33 de ces cas appartenaient au type endobronchique.

Les tumeurs se traduisent rarement par des signes cliniques et sont généralement découvertes à la suite d'un examen radiologique systématique du thorax. Elles simulent fréquemment des granulomes chroniques ou des néoplasies sur le film radiologique, bien qu'elles deviennent rarement malignes, si même elles le deviennent jamais.

L'auteur présente neuf cas nouveaux dont l'un semble être un chondrome "pur." Les tumeurs partent du tissu conjonctif de la paroi bronchique et s'étendent vers l'extérieur, dans le parenchyme pulmonaire, aussi bien que vers l'intérieur, dans la lumière bronchique. Tous ces cas d'hamartomes

étaient associés à une infiltration de cellules inflammatoires chroniques, et beaucoup furent trouvés au voisinage de zones de pneumonie chronique et de fibrose.

L'auteur suggère que l'inflammation chronique puisse constituer dans quelques cas une cause possible de l'hamartome pulmonaire.

ZUSAMMENFASSUNG

Es liegen Berichte vor über annähernd 200 Hamartome der Lunge; 33 von diesen waren vom endobronchialen Typ.

Die Tumoren geben selten Anlass zu Symptomen und werden gewöhnlich im Verlauf von routinemässigen Thorax-Röntgenuntersuchungen festgestellt. Die täuschen häufig auf den Röntgenbild chronische Granulome oder bösartige Tumoren vor, obwohl sie selten, wenn überhaupt, bösartig werden.

Es werden 9 neue Fälle vorgestellt, von denen einer ein "reines" Chondrom zu sein scheint. Die Tumoren entstanden vom Bindegewebe der Bronchialwand und dehnten sich nach aussen in das Lungenparenchym aus, ebenso wie einwärts in das Bronchiallumen. Alle diese Hamartome waren begleitet von einer Infiltration mit chronischen entzündlichen Zellen, und viele fanden sich angrenzend an Gebiete von chronischer Pneumonitis und Fibrose.

Es wird die Möglichkeit vermutet, dass die chronische Entzündung—in manchen Fällen—ein Faktor sein kann beim Zustandekommen von pulmonalen Hamartomen.

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SECTION ON CARDIOVASCULAR DISEASES

Heart Disease of Pulmonary Origin

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It behooves clinical investigators in a University Hospital group to survey from time to time, recorded clinical material on pressing diagnostic and therapeutic problems. Heart disease of pulmonary origin is a pertinent and pressing topic for, when fully developed, it has been considered hopeless by too many physicians. We have, therefore, reviewed our cases in an attempt to reemphasize precipitating and perpetuating conditions, determine predisposing factors and evaluate early diagnostic signs. We hope to touch upon possible prophylactic measures and argue for the establishment of as effective a program of management as possible. We first studied the records of 208 cases, who had been cross filed under the diagnosis of chronic cor pulmonale. It soon became apparent that minimal criteria for the diagnosis of chronic cor pulmonale had to be established, and after considerable study we arrived at those set down in Table I. We were acutely aware that chronic cor pulmonale is an end result of an insidious process. Furthermore we were fully conscious of the difficulty of arbitrarily drawing a line separating definite cor pulmonale from pulmonary disease with positional electrocardiographic changes.

The application of our criteria, as outlined here, has limited our study to patients with definite respiratory disease and pulmonary hypertension, and definite right atrial and right ventricular enlargement; as shown by the electrocardiogram or the teleradiogram. In addition, we have accepted the presence of right heart failure, without left failure, as presumptive evidence of right ventricular enlargement, even when other signs were equivocal. Patients with tricuspid or pulmonary valvular

TABLE I
CRITERIA FOR DIAGNOSIS OF PURE COR PULMONALE

1.	Evidence of Hypertension of the Pulmonary Circuit
	A. Midsternal or Epigastric Heave
	B. Pulmonary Diastolic Shock
	C. Sharply Accentuated & Split P_2
2.	Definite Evidence of Right Ventricular Enlargement
	A. ECG-Right Axis Deviation, P_2 & P_3 Tall and Sharp; High R in V_1
	B. Radiogram
	C. Right Heart Failure without Left Heart Failure
3.	Absence of Significant Valvular Lesions, Systemic Hypertensive or Ischemic Heart Disease with Myocardial Infarction
4.	Symptoms and Signs of Pulmonary Disease

Cardiovascular Service, University of Texas Medical Branch.

TABLE II
ANALYSIS OF 208 CASES DIAGNOSED AS COR PULMONALE

1. Definite Pure Cor Pulmonale	51
2. Lung Disease with Some ECG Changes, But No Demonstrable Hypertrophy or Failure of the Right Ventricle	32
3. Cases with Complications: Systemic Hypertension, Infarctions, Left Failure, etc.	60
4. Cases of Pulmonary Disease in Which Cardiac Changes were Minimal or Absent	44
5. Cases in Which the Primary Pathology was Extra Pulmonary	21
TOTAL	208

disease, constrictive pericarditis, systemic hypertension, ischemic myocardial changes and congestive failure of the left ventricle and a few rare or equivocal conditions were specifically excluded. Patients with mitral stenosis and congenital cardiac lesions were intentionally omitted, even though they were known to have increased resistance to pulmonary flow, and pulmonary hypertension. The vascular changes were secondary to heart disease and no primary lung disease was present.

Pulmonary function studies have added much to our concepts of the physiology of the cardio-respiratory system.[1, 2] However, these are mainly of value in the early detection quantitating, localizing and differentiating the pathology in the lung. Respiratory tests have been utilized only to a limited extent in studying secondary cardiac changes and were neglected in most of our cases, even though they promise much in early diagnosis.

In Table II, we have grouped the findings of our 208 cases, with which we began our study. By our criteria, there were among these 208 records only 51 indisputable pure chronic cor pulmonale cases. An additional 32 had pulmonary disease, many with various electrocardiographic findings, but in these we could not demonstrate right heart enlargement or failure. Another 60 cases were excluded at the beginning because of complicating cardiovascular diseases. In 44 the cardiac changes were insignificant and in 21 there was no evidence to substantiate pulmonary origin of the clinical picture.

In Table III, we have listed some of the unusual conditions which have

TABLE III
UNUSUAL CONDITIONS SIMULATING CHRONIC COR PULMONALE

1. Carcinoma of Lung impinging on Pulmonary Artery
2. Intracardiac Aneurysm
3. Thrombosis of Pulmonary Artery
4. Essential Pulmonary Hypertension
5. Constrictive Pericarditis
6. Tricuspid Valvular Disease

TABLE IV
AGE, SEX AND RACE OF 51 PATIENTS WITH COR PULMONALE

Age	No. of Cases	Per Cent of Total	Sex and Race	
0 - 10 years	2	4	White Male	31
10 - 20 years	2	4		
20 - 30 years	1	2	Colored Male	10
30 - 40 years	4	8		
40 - 50 years	10	20	White Female	6
50 - 60 years	15	30		
60 - 70 years	14	28	Colored Female	4
70 - 80 years	3	6		

been confused with cor pulmonale in this series. The exclusion of some of these cases may seem arbitrary, as for example, bronchogenic carcinoma impinging on the main pulmonary artery is clearly lung disease with secondary right heart failure. However, we felt it desirable to exclude those conditions without significant impairment of pulmonary function.

We have analyzed our cases in regard to age, and these data are shown in Table IV. Though there was a rather widespread distribution, the high incidence in the middle aged groups has been demonstrated. This is probably due to several factors. Lung disease must be present for a considerable time to produce changes, and the development of atheromatous degeneration will decrease cardiac reserve and serve to precipitate right heart decompensation. Two status asthmaticus deaths in two of our young patients were of great interest, these children seen in the first decade of life had mucovicidosis, with recurrent bouts of respiratory infection and with chronic bronchial infections. Both died before the age of two and incidentally, both had relative anemias instead of the polycythemias, usually present in pulmonary hypoxia.

The sex and race incidences of patients with cor pulmonale shown in Table IV indicate an overwhelming preponderance of white males in our group which is also a finding worthy of some attention. There must

TABLE V
ETIOLOGY OF 51 CASES OF PURE CHRONIC COR PULMONALE

Asthma-Bronchitis-Emphysema	33
Bronchiectasis	6
Congenital Cyst of Lung	3
Pulmonary Fibrosis	2
Pneumoconiosis	2
Coeliac Disease	2
Other Conditions	3

be more than one factor responsible for this, and we have considered a greater exposure of men to industrial dusts and colds. The higher incidence of untreated asthmatic bronchitis and of atheromatous changes in males were judged significant. The probably more frequent use of tobacco by men might appeal to some as contributing to this disproportion. We have no explanation for the racial difference except that the non-caucasions in this area, are of lower socio-economic status and might have succumbed to other causes before the full-blown cardio-pulmonary syndrome had time to develop.

In Table V, the asthma-emphysema syndrome is shown to be the principal etiology. These individuals invariably had had chronic plastic bronchitis and episodes of status asthmaticus were common. Two of them had complicating kyphoscoliosis and emphysema. The cases of congenital cysts of the lung are of interest for while they are relatively rare, they may be amenable to radical therapy, and two of the three patients have been subjected to surgical resection, with improvement. The cases of pneumoconiosis have been rare in our area but are important to note, in that they may probably be avoidable, and have been prevented by proper industrial hygiene.[3]

The Electrocardiogram in Cor Pulmonale

In analyzing in detail the electrocardiograms of these patients, we found, as was to be expected, that sinus tachycardia was extremely common, and in fact, was the predominant rhythm. It was interesting to find that the incidence of atrial fibrillation was only 6 per cent, which is rather rare in contrast to its frequency in conditions characterized by left atrial dilatation. This may be related to the lack of myocarditis in our patients. We found, in those with dilated conus arteriosus, the typical electrocardiographic picture of right axis deviation, electrically vertical position and clockwise rotation of the heart. Peaked P waves in II, III and AVF, were more frequently seen in younger patients who were not likely to have complicating myocardial disease. Evidence of right ventricular

TABLE VI

		Hematocrit	Plasma Volume	RBC Mass	Total Blood Volume
Cor Pulmonale 17 Cases	Average	56.4	+ 8.5	+48.1	+27.2
	Maximum	66.0	+37.0	+83.0	+46.0
	Minimum	48.0	—23.02	+21.0	0.0
Uncomplicated Emphysema 6 Cases	Average	43.5	+ 3.3	+ 4.3	+ 5.8
	Maximum	45.0	+12.0	+19.0	+19.0
	Minimum	40.5	— 9.0	— 8.0	— 9.0

(where possible, the values found before digitalization were used)

hypertrophy, in precordial leads was not commonly seen. The tracing of V3R, and V4R would probably have added to our evidence but these leads were not recorded routinely on most of our patients.[4] We analyzed various R:S ratios in the different leads, as well as many other possibly significant points but were unable to discover any further additions to the previous diagnostic features. Vector cardiography promises some help in the early recognition of slight right ventricular hypertrophy.

Heart Failure and Blood Mass Alterations

In 80 per cent of our 51 cases of cor pulmonale congestive heart failure was present and all of these were subsequently digitalized. It is notable that 13 (25.5 per cent) of these patients developed abnormal rhythm or other signs of digitalis intoxication sometime during our observation. This complication was probably due to efforts to push too far the cardiac

TABLE VII

BLOOD VOLUME STUDIES, PLASMA, RBC MASS AND TOTAL IN PATIENTS WITH COR PULMONALE IN FAILURE AND IN COMPENSATED STATES IN PERCENTAGES ABOVE AND BELOW NORMAL VALUES

Patient	Age	Weight Kg.	V.P. Cm. Saline	Hb. Gm. Per Cent	Hct.	P.V. I_{131}	RBC Mass Cr^{51}	Total B.V. P.V. and RBC M.
E. L. P.	42	53	18	20.1	66	+11	+83	+44
			10	19.0	64	—11	+48	+21
J. D. C.	54	87	21	19.2	61.8	+ 2	+33	+17
			11	21.5	63.3	—29	+42	+ 4
O. R.	57	53	22.5	18.0	58	+32	+95	+61
			15	15.4	40	— 5	+47	+18
R. B.	25	60	27	16.8	58.5	—18	+46	+11
C. K.	48	66	20	16.3	58.5	+37	+57	+46
C. O. D.	68	76	24	17.0	56	+16	+28	+21
W. H.	61	90	25	17.0	55	—20	+54	+14
J. A.	49	62	30+	16.5	54.8	+34	+63	+41
			31	15.4	55.2	+11	+14	+12
B. E.	59	50	12	15.6	55	— 5	+23	+20
W. E. T.	67	64	7	17.0	49	—23	+26	± 0
L. L.	42	61	28	14.2	48	+27	+21	+24
			12	14.8	50	— 1	+14	+11
E. H.	55	39	10	15.3	45	+ 3	+ 7	+19
D. D.	52	80	12	16.8	45	+ 5	+19	+11
J. C.	43	56	11	15.0	45	+ 3	+10	+ 6
A. A.	68	45	12	14.6	42	+12	+ 5	+ 9
C. W.	63	77	10	12.9	40.5	— 9	— 8	— 9
J. W. S.	35	79	11	14.5	43.5	+ 7	— 7	+ 1

glycoside to control this rather refractory form of failure.

Digitalis and diuresis of 5 of the cor pulmonale patients with failure resulted in decrease of plasma volume to below normal values. Oddly enough, the erythrocyte mass also decreased markedly in three of these cases by an average of 44 per cent while two showed no significant change. There has been subclinical jaundice demonstrated in some of these instances as evidence of a hemolytic component, but it did not seem to be of the magnitude to explain these differences. The possibility of shift of the red blood cell mass and erythrocyte sequestration were considered.

The severe cases almost invariably had polycythemia, but when we tabulated our data, the hemoglobin values ranged from 22 gms. per cent to 10.0 gms. per cent with an average of 16.1 gms. per cent which is just above the upper limits of normal for our laboratory. Nearly 40 per cent of the 51 patients had a normal value but 5, or 9.8 per cent had a complicating anemia. The results are summarized in Table VI and show the hematocrit varied from 66 per cent to 48 per cent with an average of 56.4 per cent. The venous pressure was, of course, increased in those patients with right ventricular failure. It has been noted by Reilly and by Lewis et al that the total blood volume is expanded in most cases of heart failure[6, 7] four of which had cor pulmonale.

Detailed blood volume studies on 17 of our patients were done using Cr_{51} to study the red blood cell mass by the methods of Sterling and Grey[8] and plasma volume studies were done with I_{131} by the method of Crispell et al.[9] We studied six cases with uncomplicated emphysema for comparison. The results are shown in Table VI as change in per cent above and below our normal for an individual of a similar age, sex, and body surface area. These are shown in detail in Table VII. Although there was some variation of plasma volume and only three showed a significant increase of 30 per cent or more, the red blood cell mass was consistently elevated with value ranging from +21 per cent to +83 per cent with an average increase of +48.1 per cent.

The total blood volumes were derived by addition of plasma volume and red blood cell mass and ranged from no increase to an increase of 46 per cent in the cor pulmonale patients with an average increase of 27 per cent. In contrast only four of the six emphysema patients showed increases with values ranging from —8.1 per cent to +19.0 per cent and an average of +9.0 per cent. These findings were not considered outside of the normal range.

Bronchopulmonary Measures

In the management of these patients, we would first emphasize prophylaxis, that is, control of pulmonary disease to delay or prevent cardiac changes. We have learned to practice vigorous treatments of asthmatics and desensitization to allergin if such are demonstrable.

First and foremost in management are measures aimed at alleviation of bronchopulmonary condition and any contributing focus as sinusitis or tonsillitis. We would again emphasize the value of antibacterial agents for the prompt control of bronchial infection in a primary or recurrent

flare-up. Bronchodilators, as anti spasmodics, aminophyllin, wetting agents and mucous digestants have been used frequently in recent years in our hospital. The most common plan has been a combination of aerosols as Isuprel, aerolone and Alevaire, in equal parts, either by a No. 40 De Vilbiss nebulizer, or with intermittent positive pressure oxygen apparatus of the Monaghan type. Aminophyllin (0.25-0.5 gm.) intravenously is often life saving. Abdominal pads and binders or pneumoperitoneum to elevate the diaphragm, with the hope of increasing the bellows action and augmenting the vital capacity may sometimes help. Most of our patients receive instruction in diaphragmatic breathing exercises, to increase the efficiency of the abdominal bellows.[10] All of these measures seem to add to longevity and postpone complications.

Industrial safeguards which are being more and more applied should be advocated as they will, in time, tend to reduce the incidence of pneumoconiosis and subsequent fibrosis. We have found potassium iodide in a saturated solution, carefully administered in gradually increased dosage to produce rather marked symptomatic relief in a large number of patients, particularly those with an allergic bronchitis component. Adrenal cortical steroids are apparently of some value in those allergic patients with eosinophilia, and prednisone or prednisilone would be preferable to cortisone or hydracortisone because of the decreased tendency to salt and fluid retention and potassium excretion.

Cardiovascular Procedure

Management of cardiac complications has largely been directed toward an attempt to correct myocardial failure. Venesection with blood letting until the hemoglobin is 13 gm. and the hematocrit is below 50, is usually beneficial. Digitalis, when indicated by clinical signs of failure with increased venous pressure is of value, and its efficacy may tend to vary directly with the extent to which ischemic myocardial changes complicate the picture. Mercurial diuretics are of value in reducing the hypervolemia of heart failure. Diamox has been most commonly used in these patients, because of the well known complication of respiratory acidosis and elevated CO_2.[11] We have used 250 to 500 mgs. of diamox every day or every other day, adjusting the dosage to the individual requirements. Reduction of the blood volume in acute episodes with phlebotomy has rarely been necessary, and should be done carefully. In hypervolemic polycythemic patients 500 cc. is usually sufficient to bring the hemoglobin to 12-13 gm. and the hematocrit to 45 to 50 gm.

In addition to these rather specific measures, we have advocated reduction of activity to *reduce oxygen requirements* of the tissues and a sedative as phenobarbital in moderate doses by mouth which seemingly has been of aid. Recently, the use of radio Iodine I_{131} in euthyroid patients has been advocated, in an effort to reduce metabolic needs by intentionally inducing a hypothyroid state. It would seem preferable to use drugs of a temporary antithyroid type, as propyl-thiouracil or tapezol. These agents have been used to a limited extent, and the therapy seems to be of some definite value. We have felt that the relatively heroic iodine destruction of

thyroid tissue should be reserved for the most severe cases, at least until further studies make optimal dosage a more predictable quantity.

Finally, we must briefly mention the psychotherapeutic aspect of this disease, which, in common with other chronic, progressive conditions, continues to be a significant feature from the patient's point of view at any rate. An aggressive, confident, or optimistic attitude by the doctor must be an integral part of the successful management of these unfortunate victims.

The adoption of a nihilistic attitude by the physician, can contribute as much to a patient's decline as any other factor.

Discussion

In these studies we have been impressed with the frequency of the insidiously developing pulmonary disease in patients in the wake of recurrent bronchitis. Patients are asymptomatic between attacks for 20 to 30 years because of the great 20 fold reserve of the lungs during the first phase of the disease.[12] The subsequent development of chronic hypertensive coronary artery heart disease or chronic valvular disease, may obscure the signs of predominant right heart enlargement. Under these circumstances, the pulmonary condition is often subclinical and overlooked until an acute respiratory infection precipitates symptoms.

It is certainly advantageous to the patient to have had a potential or a subclinical diagnosis prophetically made in the first phase by a wise and cautious physician, before symptoms of pulmonary origin develop, for then long postponement may be accomplished. Every recurrent or chronic cough, every asthmatic attack especially with increasing residual air in the lung, gradual decrease of exercise tolerance and fatigability, should suggest developing emphysema in the middle aged man.

The respiratory dead space increasing more rapidly than normal with aging, causes the second phase of symptoms to progress more rapidly over a period of five to eight years. The chest expansion and movement of the lung borders decrease, the timed vital capacity drops off as the residual air volume increases and the anteroposterior diameter increases slowly, almost imperceptibly. The electrocardiographic signs of right axis deviation, S1 increasing, PII and especially Vi sharpening and R developing in V1, V2 and V3, and S over the left precordium appear late. Vectorcardiography, and radiological studies help in the detection of early or slight right cardiac enlargement.

In the *third phase*, a heart disease of pulmonary origin, symptoms and signs of myocardial failure, appear and threaten dissolution within a few years. The development of pulmonary hypertension and polycythemia adds to the loudness and splitting of the P2 sound and gradually leads to the appearance of signs of right heart failure, engorged neck veins, cyanosis, enlarged liver, ascites, and edema, all of which are rather late findings. Supportive treatment, coronary vasodilators, and cardiac tonics are usually effective, for a time at least, even in this stage of chronic pulmonary disease.

However, the diagnosis and the developing cardiopulmonary process

should be made in its incipiency long before symptoms develop and steps taken to postpone the progression by prompt early vigorous treatment of the pulmonary condition. Unfortunately, the majority of patients do not present themselves until the disease is far advanced. We must be alert to the facts that every worker in a dusty trade, every asthmatic patient, every person with recurrent bronchitis, bronchiectasis, fibrosing tuberculosis, pneumonitis, sarcoidosis, bronchopulmonary disease of spirochetal, parasitic a protozoal origin, repeated sprays of pulmonary embolism[13] or cystic disease of the lung may develop primary cor pulmonale.

Secondary cor pulmonale results from capillary engorgement, alveolar edema in valvular disease as develops in mitral stenosis and in Eisenmengers complex or pulmonary valvular disease. It is necessary to rule out the presence of signs of constrictive pericarditis, or valvular disease and coronary artery lesions which may be obscured by progressive emphysema,[14] and masquerade as heart disease of pulmonary origin.

SUMMARY

1. Criteria for definite, pure, chronic cor pulmonale have been set down and 51 patients who meet these qualifications were studied. By far, the greatest incidence is in middle aged white males, though it is seen in all ages, both sexes, and in various racial groups.

2. The electrocardiogram shows the changes rather late, and in general was of relatively little value in assessing the degree of cardiac change; yet, the ecg. finding may be the first to focus attention on the presence of a right ventricular overload.

3. Detailed blood volume studies were done in 17 patients with cor pulmonale and six individuals with emphysema, using isotopes I_{131} human serum albumin to determine plasma volume, and Cr_{51} for estimation of the total red blood cell mass. The emphysema patients were not consistently abnormal, but those with definite cor pulmonale showed a variable increase of total blood volume, and a consistent increase of red blood cell mass.

4. Follow-up studies after digitalization of patients with failure showed decrease in plasma volume invariably, and frequently, a marked inexplicable decrease of red blood cell mass.

5. In management of these patients, we have strongly emphasized the importance of prophylaxis, early recognition, and energetic treatment in the early phases, even before cardiac changes are manifest. We must admit that the patients who have met our criteria represent the most advanced and refractory ones. While the long term prognosis is poor, current drugs and practices offer the patient comfort, ability to work, and probably a longer life span than was previously possible.

RESUMEN

1. Un criterio definido y puro sobre el cor pulmonale crónico se ha establecido ye se han estudiado 51 enfermos que reunieron las caracteristicas. La mayor incidencia, con mucho, se encuentra en los hombres de

mediana edad, aunque se ve todas las edades en ambos sexos y en varios grupos raciales.

2. El electrocardiograma muestra los cambios más bien tarde y en general fué de escaso valor para estimar el grado de la alteración cardiaca; sin embargo puede ser que ECG por sus cambiossea el primero que llame la atención sobre la presencia de abolsamiento del ventrículo derecho.

3. Se hicieron estudios detallados de volumen sanguíneo en 17 enfermos con cor pulmonale y en seis individuos con enfisema, usando seroalbúmina marcada con I_{131} para determinar volumen plasmático y Cr-51 para la estimación de la masa celular total de eritrocitos. Los enfermos de enfisema no fueron siempre anormales pero aquéllos con cor pulmonale definido mostraron un aumento variable en el volumen total sanguíneo y consistente aumento de la masa celular de eritrocitos.

4. El seguimiento de los enfermos después de digitalización con desfallecimiento mostró decrecimiento de volumen del plasma invariablemente y frecuentemente, un inexplicable decrecimiento del volumen celular de eritrocitos.

5. En el tratamiento de estos enfermos hemos recalcado fuertemente la importancia de la profilaxis, descubrimiento rápido, y tratamiento enérgico de modo temprano aún antes de que haya alteraciones cardiacas.

Debemos admitir que los enfermos que reunieron las características según nuestro criterio representan los más avanzados y refractarios.

Si bien el pronóstico a la larga es malo, las drogas actuales y los métodos ofrecen al enfermo confort, capacidad de trabajo y probablemente una prolongación de la vida mayor de lo que era posible antes.

RESUME

1. L'auteur a déterminé les critères qui permettent de définir le coeur pulmonaire chronique pur, et a étudié 51 malades qui entrent dans cette catégorie. La fréquence la plus grande est de loin celle des individus de sexe masculin, de race blanche, moyennement âgés, encore que cette affection soit constatée à tous les âges, dans les deux sexes, et chez divers groupes raciaux.

2. L'électrocardiogramme montre des altérations plutôt tardives et n'a en général que peu de valeur pour déterminer l'importance de l'altération cardiaque; toutefois les constatations électrocardiographiques peuvent être les premières à signaler l'existence d'une anomalies ventriculaire droite.

3. Des études détaillées sur le volume sanguin furent faites chez 17 malades atteints de coeur pulmonaire, et six atteints d'emphysème, avec détermination du volume plasmatique et évaluation de la masse totale des globules. Les malades atteints d'emphysème ne montrèrent pas constamment des anomalies, mais ceux qui étaient atteints de coeur pulmonaire montrèrent une augmentation variable du volume sanguin total, et une augmentation importante de la masse des globules rouges.

4. Des contrôles après traitement des malades par la digitaline suivi d'échec, montrèrent invariablement une diminution du volume plasmatique et fréquemment une nette et inexplicable diminution de la masse des globules rouges.

5. Dans la conduite du traitement de ces malades, l'auteur insiste fortement sur l'importance de la prophylaxie, de la découverte précoce de l'affection et d'un traitement énergique dans la phase de début, avant même que des altérations cardiaques ne se soient manifestées. On doit admettre que les malades qui répondent aux critéres que l'auteur a proposés représentent les cas les plus avancés et les plus sérieux. Bien que le pronostic à long terme soit mauvais, les drogues et médications courantes permettent d'offrir au malade un certain bien-être, la possibilité de travailler, et probablement une survie plus longue que celle qui était auparavant possible.

ZUSAMMENFASSUNG

1. Es wurden Merkmale niedergelegt für ein fest begrenztes reines chronisches cor pulmonale und 51 Kranke untersucht, auf die diese Kennzeichnung zutraf. Das bei weitem häufigste Vorkommen liegt bei weissen Männern im mittleren Alter, wenngleich man es in jedem Alter, bei beiden Geschlechtern und bei verschiedenen Rassen sieht.

2. Das Elektrocardiogramm zeigt die Veränderungen ziemlich spät und erwies sich im allgemeinen als von relativ geringem Wert bei der Bestimmung des Grades der cardialen Veränderung; der EKG-Befund kann den ersten auf den Brennpunkt gerichteten Augenmerk für das Bestehen einer Überbeanspruchung des rechten Ventrikels sein.

3. Ins Einzelne gehende Untersuchungen der Blutvolumina wurden an 17 Patienten mit cor pulmonale und 6 Personen mit Emphysem vorgenommen unter Verwendung von mit I_{131} markiertem menschlichen Serum-Albumin zwecks Bestimmung des Plasma-Volumens und von Cr_{51} zur Abschätzung der gesamten roten Blutzellmenge. Die Kranken mit Emphysem waren nicht durchweg abnormal, doch zeigten diejenigen mit ausgeprägtem cor pulmonale eine variable Zunamhe des gesamten Bluvolumens und eine damit übereinstimmende Zunahme der roten Blutzellmenge.

4. Nachuntersuchungen nach Digitalisierung von Kranken mit Versagen des Herzens zeigten eine gleichbleibende Abnahme des Plasma-Volumens und häufig eine ausgeprägte unerklärliche Abnahme der roten Blutzellmenge.

5. Hinsichtlich der Behandlung dieser Patienten haben wir besonders hervorgehoben die Wichtigkeit der Prophylaxe, frühzeitigen Erkennung und tatkräftigen Behandlung in den frühen Phasen, sogar ehe noch cardiale Veränderungen manifest werden. Wir müssen einräumen, dass die Patienten, auf die unsere Kriterien zutreffen, besonders weit fortgeschrittene und refraktäre waren. Während die Prognose auf lange Sicht schlecht ist, bieten doch die üblichen Mittel und Verfahren für den Kranken Erleichterung, Arbeitsfähigkeit und wahrscheinlich eine längere Lebensspanne als dies zuvor möglich war.

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The Fate of the Internal Mammary Artery Implant in the Ischaemic Human Heart

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The surgical treatment of coronary artery insufficiency by internal mammary artery implantation was attempted at McGill University in the animal first in 1945[1] and in man at the Royal Victoria Hospital in April 1950.[2]

The use of the pericardial fat pad graft to supplement the implant operation was first performed at the Royal Victoria Hospital in October 1953[3] on a human case of coronary artery insufficiency.

During the past 11 years much experimental evidence has been gathered to show that when an internal mammary artery is placed in the left ventricular myocardium it grows arteriolar branches which anastomose with the vast arteriolar network surrounding it within the myocardium of the left ventricle (Fig. 1A and B[4, 5, 6, 7, 8]).

These mammary-coronary anastomoses are extensive and, through them, fresh arteriolar blood is sent into the myocardium in sufficient quantity to relieve myocardial ischaemia caused by artificially produced coronary artery insufficiency.[9]

It has been repeatedly pointed out in previous publications that mammary-coronary anastomoses of large size have occurred in 46 per cent of implants placed and left in normal dog hearts, whereas, when the implanted internal mammary was left in dog hearts made ischaemic by partial ligation, or by sclerosing cellophane wrap of the anterior descending artery, the mammary-coronary rate has risen to 71 per cent.

Our experimental evidence has been confirmed in other centres when it has been carefully repeated.

There have, however, been disturbing reports concerning the failure of the internal mammary artery to anastomose with the coronary arteriolar tree in the experimental animal. In 1955 Bailey and Likoff[10] reported occlusion of implanted internal mammary arteries by thromboses. In our laboratory thrombosis of the implanted internal mammary artery has been rarely seen since 1946. Early in our experience we found that rough handling of the artery or tearing of the intercostals during separation of the artery from the chest wall favored thrombosis of the vessel. The Bailey-Likoff report was followed by Neptune[11] working with Bailey, who found mammary coronary arteriolar anastomoses in only 16.6 per

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TABLE I

INTERNAL MAMMARY ARTERY IN NORMAL ANIMAL HEARTS
13 MONTHS TO TWO YEARS FIVE MONTHS AFTER IMPLANTATION

Animal Number	Time After Implantation	Histological Estimation Of Patency Per Cent	Size of Lumen Diameter
306-32	2 Years 5 Months	18	0.32 mm.
310-1A$_4$	2 Years 5 Months	5	0.32 mm.
356-78	1 Year 8½ Months	25	0.5 mm.
368-119B$_2$	1 Year 3½ Months	10	0.2 mm.
6	1 Year 1 Month	40	0.6 mm.

cent of animals undergoing internal mammary artery implantation. However, in his series there were only two of the 18 animals in whom the artery was thrombosed. It should be noted that Neptune's animals were studied after the artery had been left nine months in a normal non-ischaemic ventricular myocardium.

FIGURE 1A

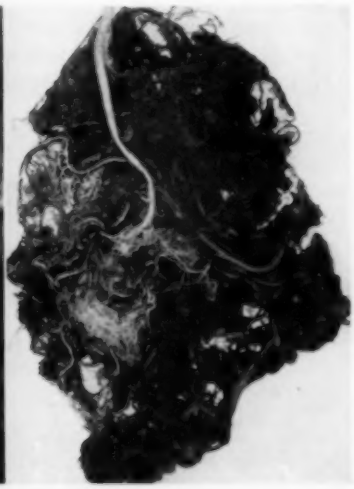

FIGURE 1B

Figure 1A: Digestion cast of implanted internal mammary artery made 12 days after implantation. Observe the fine arterial buds in tunnel.—*Figure 1B:* Digestion cast of implanted internal mammary artery made 7 months after implantation, and 5½ months after ligation of anterior descending branch left coronary artery (128B$_4$). Measurement of diameter of casted mammary artery and arterial lumina by dissecting microscope:

Internal mammary artery		
	at entrance to heart	2.25 mm.
	before branching	2.0 mm.
	after branching	1.5 mm.
(Total of 7 branches)		
Anterior descending branch left Coronary artery		2.25 mm.

More recently Bakst *et al* and Bailey[12] have studied internal mammary arteries six months after implantation into normal dog hearts. Backflow studies made on the anterior descending branch of the left coronary artery indicated that the internal mammary artery in their animals failed to augment the collateral circulation. The authors concluded that: "It has become strikingly obvious that in these experiments the internal mammary artery implant failed to contribute any measurable amount of blood to the anastomotic flow of the left anterior descending artery. It was further obvious that the collateral blood flow from the left anterior descending artery originated almost entirely in the unoccluded left circumflex despite the presence of a patent internal mammary implant."

This statement is most misleading, particularly in the light of a second statement by the same author two paragraphs later in the same article: "In each of these specimens an obliterative endarteritis largely occluded the lumen of the implanted vessel within a period of six months. It was obviously impossible for a physiologically significant quantity of blood to flow through these vessels."

It is difficult to understand how Bakst *et al* and Bailey expected that their internal mammary implants would contribute blood to the myocardium when they were almost completely blocked. The results reported by these authors differ greatly from those obtained in our laboratory for two major reasons. The first of these is technical. It is perfectly obvious from the published drawings that although the authors mention the

TABLE II

DIGESTION CAST STUDIES OF INTERNAL MAMMARY ARTERIES IN ISCHAEMIC HEARTS FIVE, SIX, AND SEVEN MONTHS AFTER IMPLANTATION

(All vessels measured by dissecting microscope)

			Internal Mammary Artery Diameter		
Number	Anterior Descending Diameter	Circumflex Diameter	Entrance Heart	Myocardial Tunnel Before Branching	After Branching
33W	1.1 mm.	1.0 mm.	1.3 mm.	1.0 mm.	0.5 mm.
128B.	2.25 mm.	....	2.25 mm.	2.0 mm.	1.50 mm. Total 7 branches
521B.	1.0 mm.	1.75 mm.	1.5 mm.	1.25 mm.	0.75 mm.
504	1.75 mm.	1.5 mm.	1.25 mm.	0.75 mm.	0.75 mm. Many branches
14W	1.25 mm.	1.0 mm.	1.5 mm.	1.25 mm.	0.75 mm. 3 branches
1F	1.25 mm.	....	1.12 mm.	1.12 mm.	1.0 mm.

Note small difference between size of internal mammary artery outside heart and in tunnel.

Most arteries were as large as anterior descending at its origin.

All animals survived anterior descending branch ligation 6 weeks after implantation.

TABLE III

STUDY OF SEVEN HUMAN INTERNAL MAMMARY ARTERIES 60 HOURS TO 18 MONTHS AFTER IMPLANTATION

		Per Cent
Total number of cases	7	
Number of patent arteries	6	85.8
Number of thrombosed arteries	1	14.2

(Arteries examined from 60 hours to 18 months after implantation)

avoidance of angulation of the internal mammary artery, they were unaware of the importance of making the myocardial tunnel so that it is in line with the point of the artery's attachment to the sternum (Fig. 2). Failure to observe this technical point causes angulation of the artery at

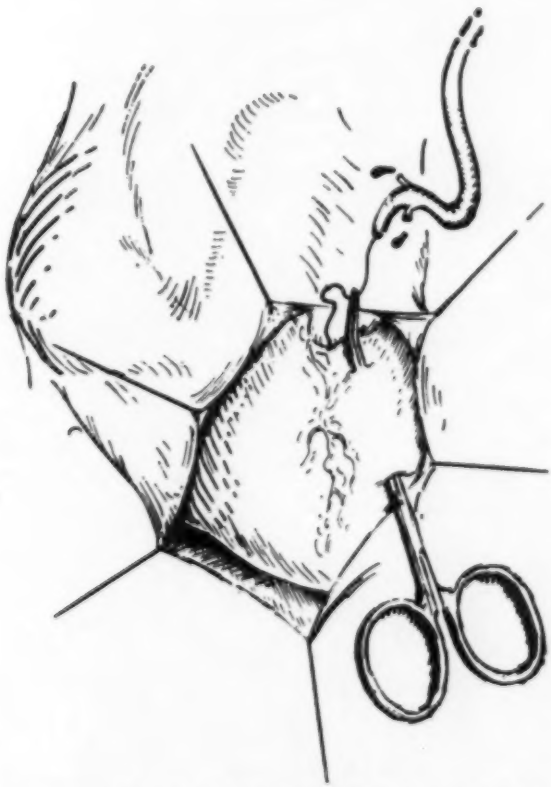

FIGURE 2: Reproduction of drawing published by Bakst *et al* and Bailey, of internal mammary artery implant. *Note* how direction of tunnel is placed in different plane to internal mammary artery on chest wall, which favours angulation, narrowing, and final obliteration of implanted vessel.

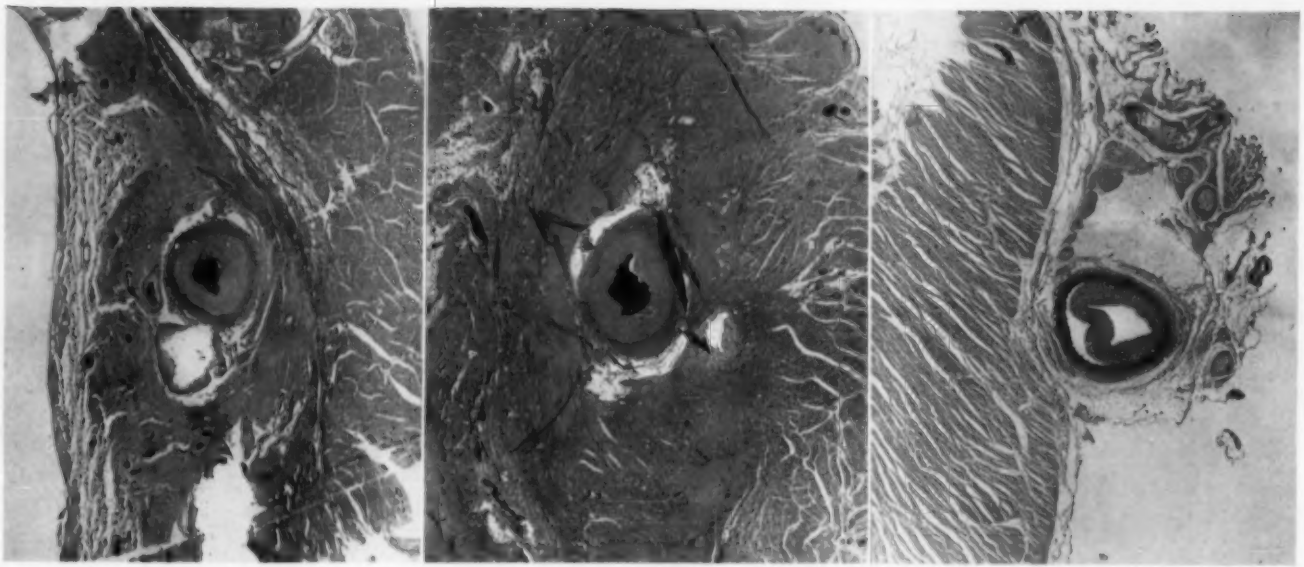

FIGURE 3A FIGURE 3B FIGURE 3C

Figure 3A: Microphotograph of animal No. 306, section 32 of internal mammary artery left in normal canine heart 2 years 5 months. Lumen 18% open, measuring approximately 0.4 mm.—*Figure 3B:* Microphotograph of animal No. 356, section 78 of internal mammary artery left in normal canine heart 1 year 8½ months. Artery lumen 25% open, measuring approximately 0.5 mm. —*Figure 3C:* Microphotograph of animal No. 6, 13 months after implantation into normal heart. *Note* 40% arterial lumen, measuring approximately 0.6 mm. at entrance to heart.

TABLE IV

OPERATIVE MORTALITY—INTERNAL MAMMARY ARTERY IMPLANTATION IN THE TREATMENT OF CORONARY ARTERY INSUFFICIENCY

		Per Cent Mortality
Total number of cases	54	
Angina decubitus—15 cases with 9 deaths		60
No angina at rest—39 cases with 3 deaths		7.6

The total deaths include the first patient operated upon in each of four different Montreal hospitals, all of which were cases of severe angina decubitus.

its point of entrance into the myocardium, resulting in arterial occlusion by thrombosis or intimal proliferation. Not only have these authors failed to follow the details of internal mammary implant technique frequently described by us, but they have failed to repeat carefully our experimental methods. Thus we find that the implanted internal mammary arteries described by Bakst *et al* and Bailey had been left in the myocardium of normal hearts. These implants were in competition with normal coronary arteries. Little wonder that they report the lumina of the implanted vessels were 95 per cent obliterated by severe intimal proliferation.

FIGURE 4: Digestion cast of internal mammary artery made 5 months after implantation and 4 months after anterior descending branch ligation. Measurements by dissecting microscope showed lumina as follows:

Anterior descending branch left Coronary artery	1.1 mm.
Circumflex	1.0 mm.
Internal mammary artery at	
Entrance to heart	1.3 mm.
before branching	1.0 mm.
after branching	0.5 mm.

In our series, many hundreds of animals have been studied after internal mammary artery implantation. These can be divided into two groups, namely, those in which the artery was implanted and left in a normal non-ischaemic heart, and those in which the artery was implanted and left in an ischaemic heart. In the first non-ischaemic group, our implants developed intimal proliferation. Rarely, however, has there been the extensive intimal proliferation reported by Bakst *et al* and Bailey. When it did occur, there was some mechanical factor, such as angulation, or a partial mural thrombus, which narrowed the internal mammary artery thus reducing the rate of blood flow through its channels and favouring intimal proliferation.

In the absence of arterial thrombosis or angulation it is true that intimal proliferation does occur, but rarely to the extent of obliterating 95 per cent of the arterial lumen. In Table I are listed five animals studied 13 months to two years five months after implantation. In all of these the internal mammary artery was left in a normal heart which did not need it and the arterial lumina remained from 10 to 40 per cent open. The largest lumen was 0.6 mm. and the smallest 0.2 mm. All showed mammary-coronary anastomoses. Certainly four out of five had lumina large enough to supply a helpful amount of blood to the left ventricle (See Fig. 3A, B, C).

In the second group of animals the internal mammary arteries were left in position for many months in hearts rendered ischaemic by ligation of the anterior descending artery branch six weeks after internal mammary implantation. The fate of the implanted internal mammary arteries left in seven ischaemic hearts is shown in Table III. Five, six and seven months later flow studies were made and the rate of blood flow through the implants determined.[9] Digestion casts of the cardiac circulation were

TABLE V

RESULTS OF CORONARY ARTERY INSUFFICIENCY TREATED BY INTERNAL MAMMARY ARTERY IMPLANTATION IN 49 PATIENTS FOLLOWED SIX MONTHS TO 5½ YEARS

	Before Operation					After Operation							
	Number of Patients	Totally Disabled		Survived		No Pain or Slight Pain		Less Pain		The Same or Worse		Returned to Work	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
No angina at rest	35	26	74.3	32	91.7	23	65.7	3	9.3	8	21.8	30	85.7
						—75%—							
Angina decubitus	14	14		7		3	21	1	7.1	3	21	4	28.5

5 patients with no angina at rest have died months to years after operation.
27 (77.1%) of this group are still alive; 23 (65.7%) have no pain or less pain.
27 (77.1%) still work.

made by injecting the internal mammary artery and coronary vessels with different coloured plastics. Using the dissecting microscope, the cast diameters of eight transplanted internal mammary arteries were measured at the entrance to the heart, and before and after branching. Note how the arteries maintain their lumina in six out of eight animals. The arteries were patent with small anastomoses in two. The internal mammary artery remained open in all eight animals (100 per cent).

A comparison between the diameter of the lumina of the anterior descending branch, circumflex, and internal mammary arteries as outlined by the casts made of them, is of interest. In three out of six, the diameter of the lumen of the internal mammary artery outside the heart was greater than the anterior descending branch of the left coronary at its origin. It was equal in one, and slightly less in two. There is slight reduction in the size of the internal mammary vessel after entrance into the myocardial tunnel, and marked reduction after it has given off its many new branches. In the casts the branches can be seen to join with arterioles of the myocardial arteriolar network.

These arteries were left in ischaemic myocardia. Obviously there was

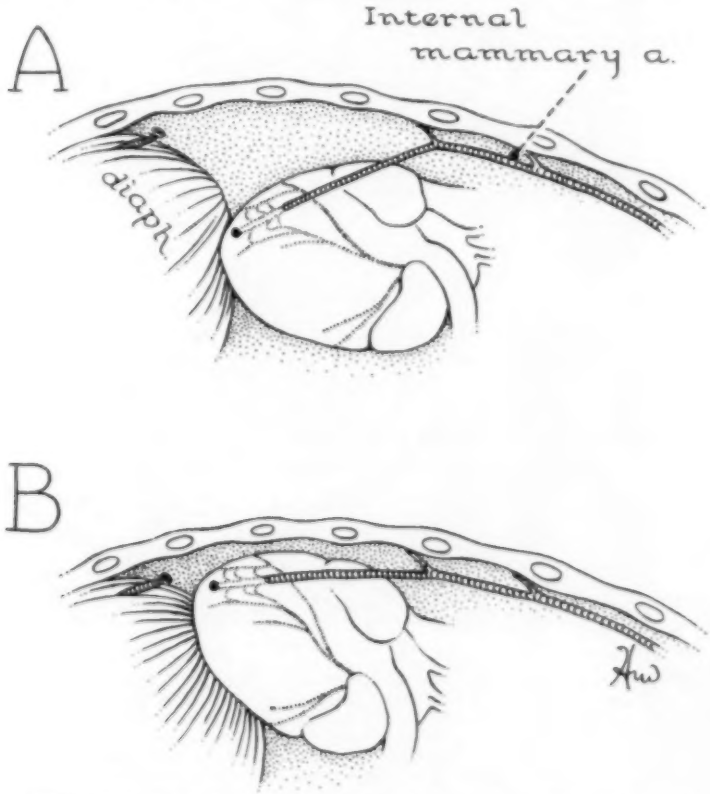

FIGURE 5: Method of placing internal mammary artery in tunnel.

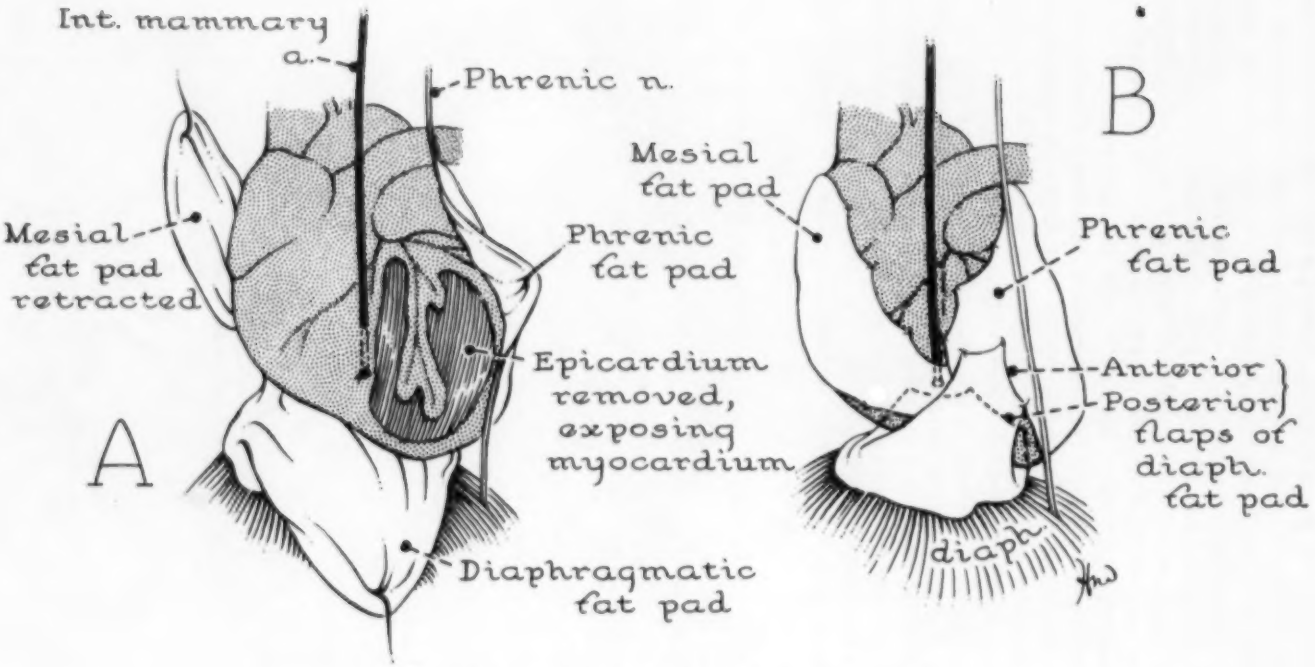

FIGURE 6: Technique of pericardial fat pad graft.

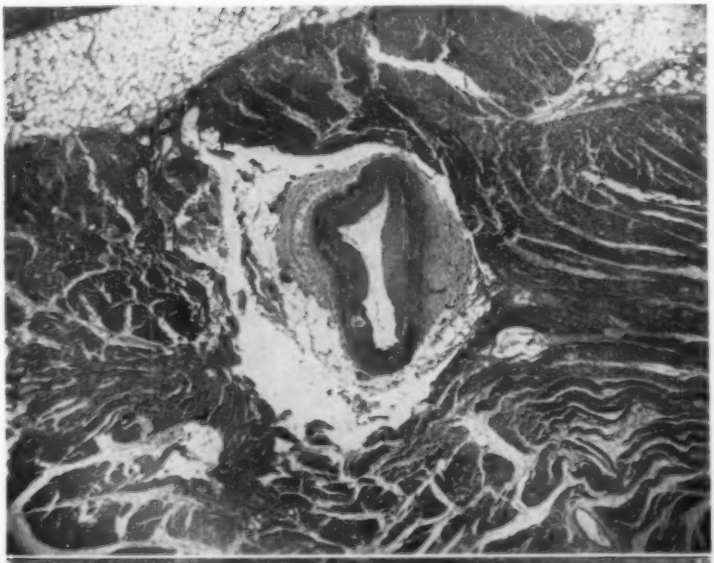

FIGURE 7

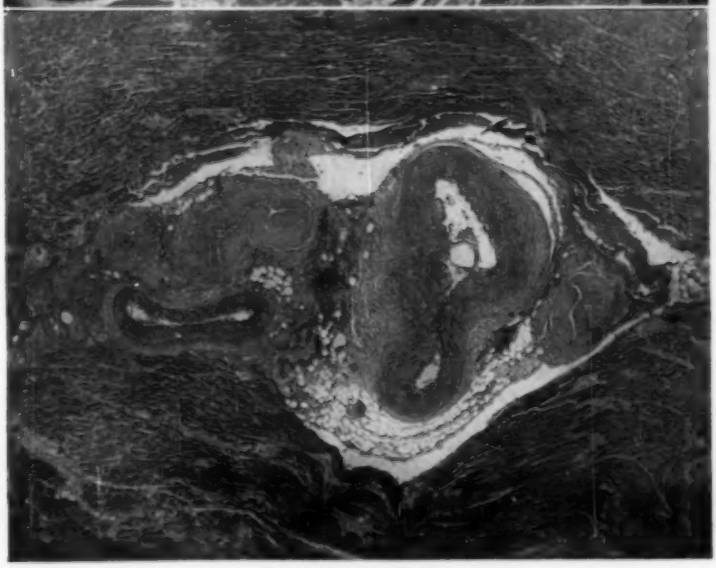

FIGURE 8

Figure 7: Microphotograph of human internal mammary artery lying within the myocardium 62 hours after implantation. *Note* open arterial lumen and absence of haematoma. There is little reaction surrounding the vessel other than a small zone of muscle necrosis.—*Figure 8:* Microphotograph of human internal mammary artery 60 hours after implantation with second vessel alongside of it—presumably the 6th intercostal artery. Again there is no haematoma, and there is a small area of muscle necrosis about the implant.

no marked obliteration of their lumina. The flow rate through these vessels has been published[9] and was satisfactory. In one animal (Fig. 4) it reached 55 cc. per minute, compared to a normal left coronary artery of cc. per minute in dogs of this size.

In the human suffering from severe anginal pain due to coronary artery disease, there is ischaemia of the ventricular myocardium. We have studied one example in which an internal mammary artery placed in this type of muscle had not been closed off by intimal proliferation when examined 18 months later.

In our series of 54 human patients operated upon for coronary artery insufficiency, we have studied at necropsy seven implanted human internal mammary arteries 60 hours to 18 months after implantation. A brief report of the pathological findings will be given but, before presenting the material, it might be well to briefly outline the operative procedure in order that the histological data may be more readily understood.

The Vineberg Operation for Coronary Artery Insufficiency

There has been little variation in the technique of internal mammary artery implantation since 1950.[13] The operation (Fig. 5) consists of freeing the left internal mammary artery from the chest wa'l by ligating and transecting the intercostal branches between the fourth and sixth interspaces inclusively. The internal mammary artery thus freed from the

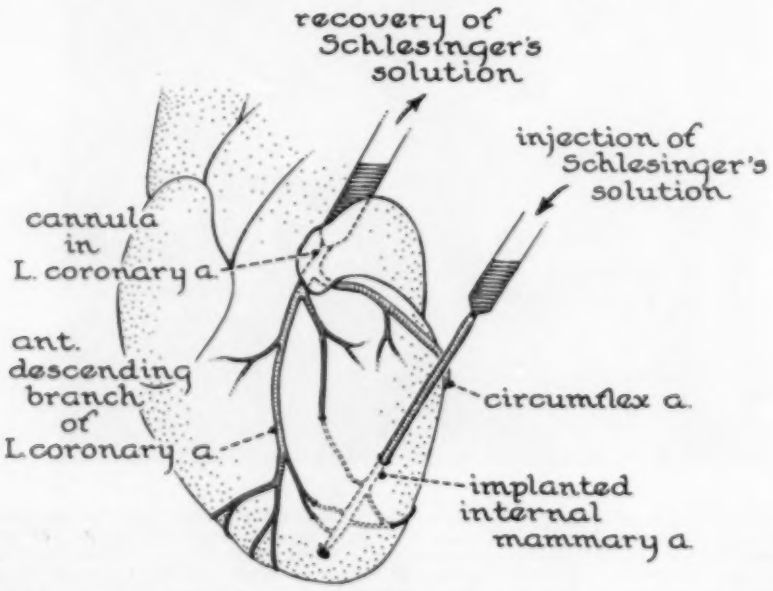

FIGURE 9: Standard method of injecting internal mammary artery through cannula in internal mammary artery. Injection mass returns through cannula placed in left coronary artery.

chest wall is transected between two ligatures distal to the sixth interspace. The proximal free end of the artery is pulled into a tunnel made in the wall of the left ventricle. Before it is drawn into this tunnel, the sixth intercostal artery is cut so that blood escapes freely through it from the internal mammary artery into the surrounding myocardial tunnel. The open sixth intercostal or slit into the side of the internal mammary artery allows the blood to move down and out of the artery: the peculiar sponge-like character of the myocardial vessels assures that the blood which escapes from the implanted internal mammary artery is carried away. By this technique arterial blood reaches the myocardium immediately, and within three to four weeks through arteriolar mammary-coronary anastomosis. Slowing of the blood flow through the implanted vessel due to angulation or mural thrombus favors thrombosis and intimal proliferation. There is evidence to indicate that the extent of the intimal proliferation in the implanted vessel is directly proportional to the rate of blood flow through it.[13]

In October 1953 the standard Vineberg implant procedure was supple-

FIG. 10A

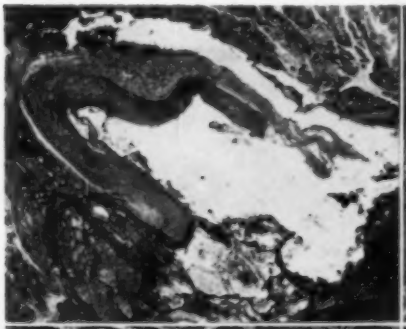

FIG. 10C

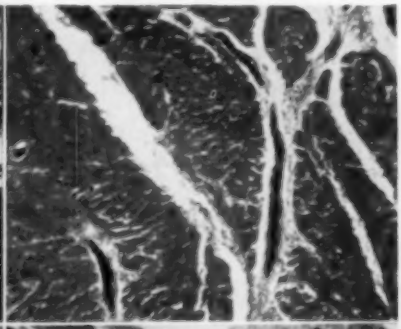

FIG. 10B

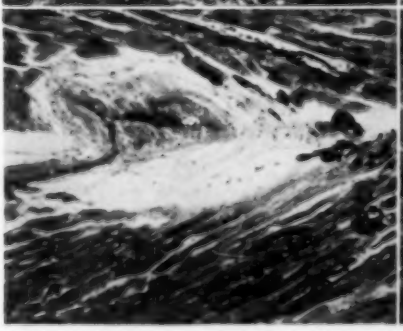

FIG. 10D

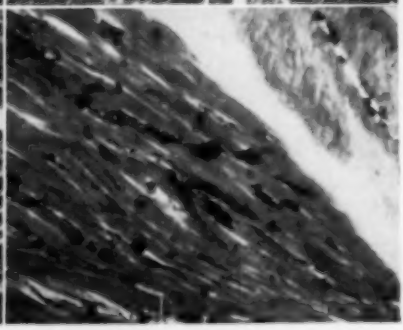

Figure 10A: Internal mammary artery in myocardium of human case of angina decubitus. This patient died 82 hours after implantation, from intractable bronchial spasm following penicillin injection. At autopsy, the internal mammary artery was injected with India ink. *Note* the slit in the arterial wall, with India ink in the space surrounding the vessel. There is no haematoma.—*Figure 10B: Note* India ink filling the arterioles within the myocardium distant to the implant.—*Figure 10C* and *D:* Same patient as in Figure 10A and B. C, note how the India ink is lying in large spaces between muscle bundle groups. These may be myocardial sinusoids filled with India ink. D, note how the India ink injected through the internal mammary artery has reached the capillaries which lie between muscle fibres.

mented for the first time by pericardial fat pad grafts in a human case of coronary artery insufficiency.[3]

The technique of the pericardial fat pad graft is simple (Fig. 6). The mediastinal, diaphragmatic, and phrenic fat pads are reflected from the surface of the fibrous pericardium and left attached to their respective blood supply. The fibrous pericardium is removed over the entire antero-lateral and part of the posterior surfaces of the left ventricle. Following internal mammary artery implantation, various areas of the epicardium are removed by sharp dissection from the antero-lateral and posterior surfaces of the left ventricle. This denudes the myocardium so that the raw vascular surfaces of the pericardial fat pads are placed in direct contact with myocardial muscle fibers and the many vascular spaces lying between the muscle fibers and bundles. The value of the pericardial fat pad as a source of myocardial blood flow has been studied since that time in the experimental laboratory.* A report of that study is now being prepared: it would seem that the pericardial fat pad is capable of supplying blood to an ischaemic myocardium. In the seven cases about to be described, a careful study of the pericardial fat pad was made in one patient.

Case 1: 62 hours after internal mammary artery implantation. The first human case of coronary artery insufficiency to undergo internal mammary artery implantation was operated upon in April 1950. The patient, a 53 year old tailor, had been totally disabled for 36 months due to severe angina at rest, without exciting cause. A true case of angina decubitus, he had experienced both anterior and posterior wall infarctions. He made an excellent recovery from his operation but died suddenly 62 hours later. Autopsy showed that he had been living on a pin-point opening in the circumflex artery, which had become blocked by a fresh thrombus. A section through the site of implantation of the internal mammary artery is shown in Fig. 7. The implanted internal mammary artery was widely open. There was no evidence of haematoma in the myocardial tunnel about the implanted artery, even though the

*Experimental Laboratory of the Montreal Heart Institute, and Department of Experimental Surgery, McGill University.

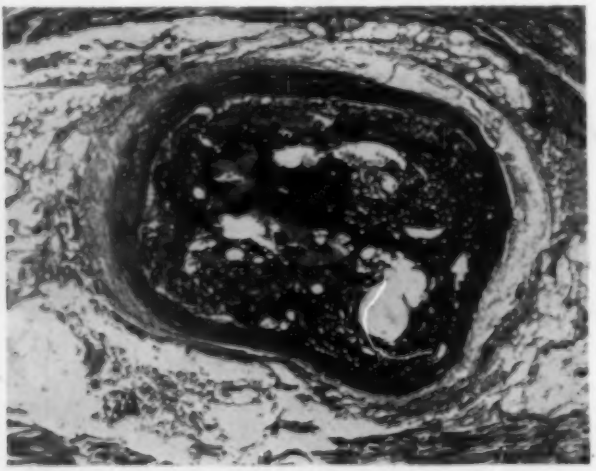

FIGURE 11: Microphotograph of internal mammary artery 96 hours after implantation into ischaemic heart. *Note* patent internal mammary artery containing India ink mixed with blood in its lumen.

artery had been placed in the tunnel with an attached bleeding sixth intercostal vessel. There was a small zone of myocardial muscle necrosis surrounding the vessel with little other reaction to the implanted vessel.

Case 2: 60 hours after internal mammary artery implantation. The second human internal mammary artery to be studied after implantation into the left ventricular myocardium was that of a 57 year old man. The patient, a civil servant, had been disabled for 36 months and, like our first patient, suffered angina at rest, without exciting cause. This second case of angina decubitus, like the first, had experienced both anterior and posterior wall infarctions prior to surgery. He, like the first patient, died suddenly 60 hours after operation from a fresh thrombus blocking a circumflex artery—apparently the only vessel open in his heart.

A section through the site of implantation is seen in Fig. 8. The internal mammary artery is widely patent, with a large patent artery alongside of it, presumably the sixth intercostal artery. There is no surrounding haematoma. There is a small area of muscle necrosis about the implant, similar to that seen in the first patient.

Case 3: 82 hours after internal mammary artery implantation. This 44 year old janitor, had been disabled by angina decubitus for four years, and had suffered both anterior and posterior left ventricular infarctions. He underwent operation successfully, but died 82 hours after implantation of the internal mammary artery and pericardial fat pad grafts. Death was caused by severe, intractable bronchial spasm which followed a penicillin injection three hours prior to his demise. At autopsy the internal mammary artery was injected with India ink proximal to its entrance into the myocardial tunnel (Fig. 9). This injection was made in the presence of a senior pathologist* who watched the coronary vessels of the left ventricle fill with the India ink injected through the internal mammary artery which had been implanted into the left ventricular myocardium 82 hours previously. There was no injection of the pericardial fat pad.

In this patient, just prior to pulling the internal mammary artery into the myocardial tunnel, the sixth intercostal had been cut but did not bleed satisfactorily. It was necessary to cut a hole in the wall of the internal mammary artery at the point of junction between it and the sixth intercostal vessel. This opening in the side wall of the implanted internal mammary artery is clearly visible in Fig. 10A. Apparently the India ink introduced into the internal mammary artery proximal to the heart left the artery through this hole and entered a larger space around the artery which had been created by spreading the muscle bundles when making the myocardial tunnel to receive the implant. From here the India ink had reached arteries (Fig. 10B), endothelial lined spaces between muscle bundles (Fig. 10C), and capillaries lying about muscle fibres (Fig. 10D). The exact mechanism of how this happens at this stage has not been proved to our satisfaction. However, it appears likely that the ink first escapes from the implanted internal mammary artery into the surrounding space created by the making of the myocardial tunnel. From this area it is carried to endothelial lined spaces lying between muscle bundles (Fig. 10C). These spaces may be the myocardial sinusoids described by Wearn[14] which are in communication with arterioles and capillaries.

Case 4: 96 hours after internal mammary artery implantation. A 60 year old man, was completely disabled for seven months because of angina decubitus following several coronary occlusions with infarction. In addition to this severe coronary artery insufficiency, he suffered from diabetes and hypertension. Four days after operation the patient, who had been doing well, died suddenly. Death was caused by a fresh thrombus occluding the right artery.

Examination of the implanted internal mammary artery showed it to be completely patent (Fig. 11). It should be noted that the narrow zone of necrotic myocardial muscle surrounding the implant is beginning to show healing and organization. Unfortunately, in this patient India ink was not injected into the implanted internal mammary artery as was done in our third case.

Case 5: 10 days after internal mammary artery implantation. This 44 year old man, had suffered two coronary artery occlusions, with infarction. He had experienced left-sided hemiplegia with almost complete recovery of the latter. His exercise tolerance was limited to two blocks because of anginal pain. He had been totally disabled for two years, but was not a case of angina decubitus. The post-operative course of this patient is important in the light of the findings at autopsy. He did not receive Wangensteen suction, although it is a routine procedure in all patients operated upon for coronary artery insufficiency. On the fourth post-operative day there was marked abdominal distension and vomiting due to paralytic ileus. It took three days to partially control this complication. On the 10th post-operative day he died suddenly from occlusion of the artery by a fresh thrombus. At autopsy the apex of the heart was elevated and displaced laterally by the raised diaphragm. This shift of the

*Dr. Paul Mailloux, Senior Pathologist, Montreal Institute of Cardiology, Montreal, Canada.

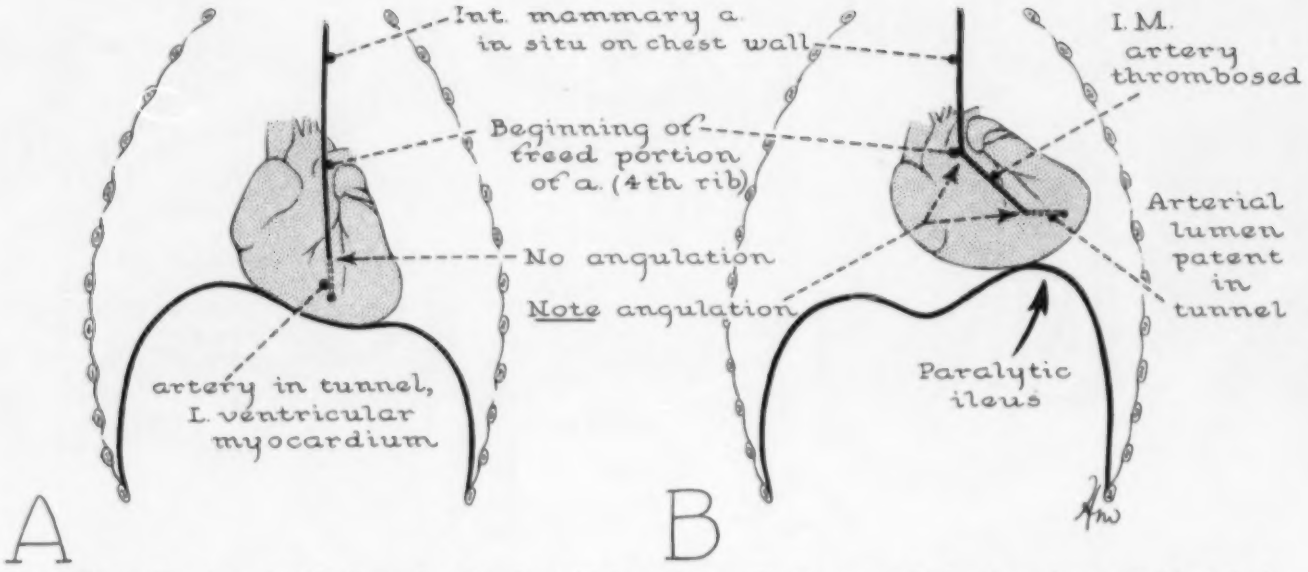

FIGURE 12: The above sketch indicates how the elevated left diaphragm tilts the apex of the heart, causing angulation of the implanted internal mammary artery. Angulation of artery resulted in thrombosis of vessel.

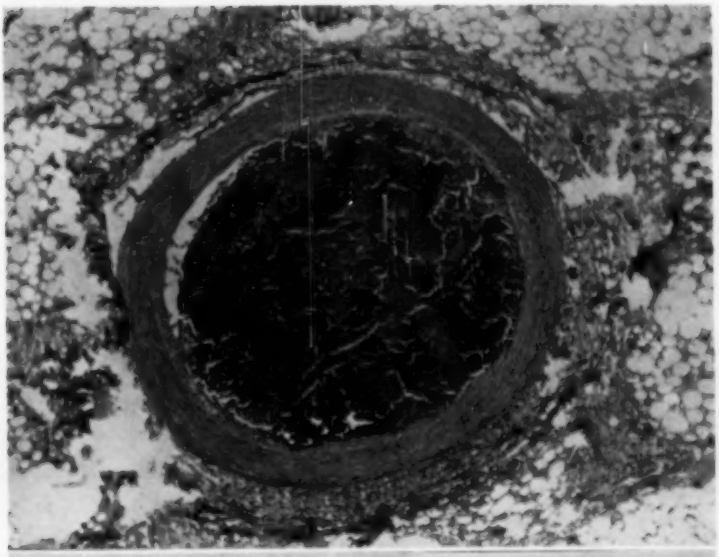

FIGURE 13

FIGURE 14

Figure 13: Microphotograph of human internal mammary artery 10 days after implantation, with 6 day old thrombus (estimated age) occluding its lumen. *Note* relationship between peak of paralytic ileus 4 days post-operative and estimated 6 day age of thrombus.—*Figure 14:* Microphotograph of section made through intramyocardial portion of same artery shown in Figure 13. *Note* artery in Figure 13 *outside* heart is thrombosed due to angulation, whereas same artery lying *in* heart shown above is patent.

FIGURE 15A

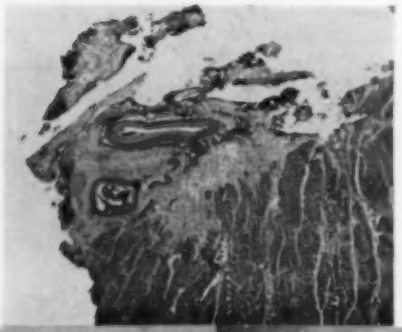

FIG. 15B

FIG. 15C

FIG. 15D

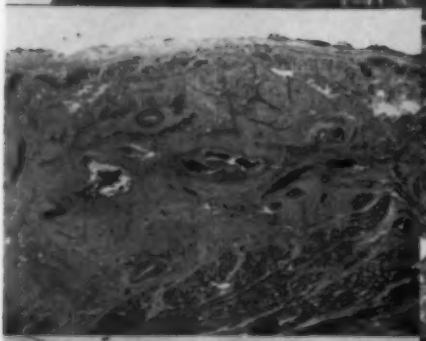

FIG. 15E

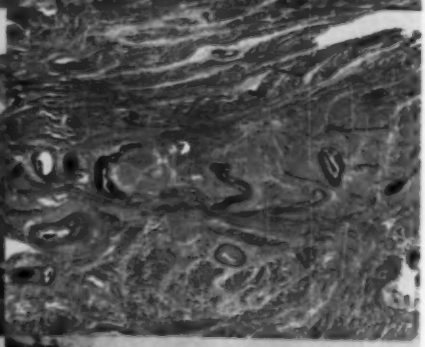

FIG. 15F

FIG. 15G

longitudinal axis of the heart into an almost transverse position in the thorax had resulted in acute angulation of the internal mammary artery at the chest wall and at its entrance into the heart (Fig. 12). The internal mammary artery was thrombosed (Fig. 13) in that portion proximal to its entrance into the heart. It was patent within the myocardial tunnel (Fig. 14). The duration of the thrombus was estimated, pathologically, to be not more than six days. It was four days after operation that the paralytic ileus, with abdominal distension and elevation of the left diaphragm, was discovered and treated. Six days later the patient died. Since the thrombus in the internal mammary artery was estimated to be not more than six days old, it is reasonable to assume that it developed as a result of the angulation brought about by the upward and left lateral displacement of the heart through abdominal distension. The clinical observation corroborates our frequently reported observations in animals concerning the disastrous effect of angulation on implanted internal mammary artery patency.

Case 6: 18 months after internal mammary artery implantation and pericardial fat pad graft. The last patient, a 60 year old aircraft worker, suffered from angina decubitus, requiring 300 nitroglycerine tablets per week. He had had two attacks of

FIGURE 16: Microphotograph of pericardial fat pad graft showing injection of vessels with India ink from retrograde circumflex artery injection.

At left:

Figure 15: Microphotographs of serial sections taken through implanted human internal mammary artery 18 months after implantation.—*Figure 15A:* Before tunnel. Here the internal mammary artery is seen lying on the surface of the left ventricular myocardium. It is flattened due to deep-freeze packaging which resulted in flattening of the entire specimen. It is widely open and shows little or no intimal proliferation, and the lumen contains India ink which was injected through the circumflex artery.—*Figure 15B:* Entrance to Tunnel. The artery is seen at the beginning of the tunnel, widely open, with India ink in another myocardial vessel.—*Figure 15C:* First 1/4 of tunnel. Shows artery branching within the myocardium. The branches contain India ink. Again there is no evidence of intimal proliferation.—*Figure 15D:* First 1/3 of tunnel. In this area the artery breaks up into arteriolar branches and many almost cavernous-like cavities containing India ink.—*Figure 15E:* Centre of tunnel. The artery can no longer be identified. It has broken up into numerous branches containing India ink, and two vessel complexes one of which slowly disappears when followed through the tunnel. The other continues branching and eventually reconstitutes itself as an artery.—*Figure 15F:* Last quarter of tunnel. Here one sees the artery after reconstitution. It is open, still branching, and shows no evidence of intimal proliferation.—*Figure 15G:* End of tunnel. The artery is still open, and branching at the very end of the tunnel. It contains India ink which was injected, retrograde, through the circumflex artery.

coronary artery thrombosis with resultant antero-lateral and posterior wall infarctions. On November 18th, 1953, he underwent internal mammary artery implantation and pericardial fat pad graft. Four months after operation he was able to walk a distance of one to two miles without pain, and resumed his work as an aircraft worker on an eight-hour night shift. He continued in good health, experiencing only occasional substernal pain after marked effort. In may 1955 he developed intestinal obstruction and died. There was no evidence of cardiac disability. Death was due to cancer of the pancreas. The patient had requested that, after death, his heart be sent back to Montreal. It was received in a deep-freeze package. The internal mammary artery could not, at first, be identified, so India ink was injected into the circumflex artery in a retrograde manner. The internal mammary artery was then identified and was found to contain India ink, as did the diaphragmatic fat pad which had been placed on the myocardium at the time of operation 18 months before.

Over 800 microscopic serial sections of the implanted internal mammary artery, which had been left in an ischaemic human heart for 18 months, were studied. Through this study certain facts were definitely established. There was little doubt that this particular internal mammary artery had been implanted into an ischaemic human heart. There was diffuse myocardial fibrosis, and marked narrowing of all three major coronary vessels. The internal mammary artery had been implanted into a shallow one inch tunnel in the anterior wall of the left ventricle. The condition of the artery in the tunnel and its branches has been made clear as a result of the extensive serial section study made by the authors. Unlike the many arteries examined in our animal series, this human artery shows no intimal proliferation distal to its points of branching. It has a normal lumen throughout. Representative microscopic sections of the implanted internal mammary artery as it passes through the myocardial tunnel have been selected at different levels. Thus, in Fig. 15A, the internal mammary artery is seen lying on the surface of the left ventricle before entering the myocardial tunnel. It appears flattened due to squeezing of the entire specimen as the result of deep-freeze shipment. It should be noted that the lumen is almost completely normal and shows little intimal proliferation. It contains India ink, injected retrograde through the circumflex artery. As the artery enters the tunnel, Fig. 15B, there appears to be no narrowing or pinching of the vessel. Fig. 15C shows the artery one quarter of the way along the tunnel, with many branches containing India ink. In the first third of the tunnel the artery breaks up into arteriolar branches and into many almost cavernous-like cavities which contain India ink. In the central portion of the tunnel the vessel divides into two main complexes, Fig. 15E, one of which when followed through the tunnel branches and disappears; the other continues to branch and eventually reconstitutes itself into the artery, Fig. 15F. Perhaps the strangest fact is that the vessel is still open and branching at the very end of the tunnel, Fig. 15G. Even here there is no evidence of intimal proliferation.

Pericardial fat pad graft:

At the time of retrograde circumflex injection, India ink was seen entering the vessels of the diaphragmatic fat pad. This had been grafted to the left ventricular myocardium at the time of operation after careful removal of the epicardium. Microscopic examination of the point of contact between the fat pad graft and the heart muscle is seen in Fig. 16. There is little fibrous reaction at the graft site, and there are many vessels of fair size lying in the fat pad graft which contain India ink which had been injected retrograde through the circumflex artery.

DISCUSSION

The condition of the seven internal mammary arteries examined is shown in Table III. Of the seven vessels only one was thrombosed, i.e. 14.2 per cent and 85.8 per cent remained open. One was examined 18 months after implantation and showed no evidence of intimal proliferation.

Apparently, communications between the implanted vessel and myocardial sinusoid-like spaces are established as early as 82 hours. This is long before actual branching occurs, since we know from animal digestion casts that the artery only starts to bud around the 12th day after implant, and does not form true arteriolar branches before three to four weeks.

Further, we know that in the human, as in the animal, the implanted internal mammary artery forms mammary-coronary anastomoses by sending out arteriolar-like branches within the myocardium. These are known to have persisted for 18 months and did not disappear after a few weeks —as has been suggested by Glenn.[15] Certainly, in the patient in whom the artery was left in an ischaemic heart for 18 months, there was no appreciable evidence of the intimal proliferation reported by Bailey, Bakst *et al*, in animals. In fact, the artery remained open for the entire length of the tunnel. This has never occurred in internal mammary artery implants in animals, even in hearts rendered partially ischaemic by anterior descending branch ligation. Usually, the portion of the internal mammary artery distal to the point of branching shows varying degrees of narrowing of the lumen due to intimal proliferation in the animal heart, even though there is little or none proximal to the point of branching within the tunnel.

In our animal studies we have shown that the direction of blood flow through the implanted internal mammary artery is *into the heart* and not from the heart into the internal mammary artery.

In a patient such as the last, who was totally disabled by angina decubitis prior to implant, and in whom pain disappeared and there was marked increase in exercise tolerance, there can be little doubt that his heart received extra-cardiac arterial blood through the patent, branching implanted vessel.

In our series of 54 internal mammary artery implants in human cases of coronary artery insufficiency, 74 per cent were totally disabled by anginal pain and 84 per cent had had one or more known infarctions prior to surgery.

No patient was operated upon as a preventive measure. All except one suffered from anginal pain.

We cannot agree with Beck and Leighninger[16] who state that "any patient in whom the diagnosis of this disease" (coronary artery insufficiency) "is established is a candidate for operation providing the disease has not advanced to a point where risk of operation is too great."

In our series 15 of the group suffered angina decubitus. Of these nine died—a 60 per cent mortality. There were 39 patients with no angina at rest. Of these three died—a 7.6 per cent mortality (Table IV).

Of 49 patients followed six months to 5½ years (Table V), 30 had no angina at rest; 74 per cent of these were totally disabled prior to surgery, and 85.7 per cent became pain-free or had slight pain. There were 14 cases of angina decubitus, 21 per cent of whom became pain-free or had slight pain, and 28 per cent returned to work after internal mammary artery implantation and pericardial fat pad graft.

SUMMARY

Evidence has been presented to show that the internal mammary artery implanted into the human heart that is ischaemic as a result of coronary artery disease, remained open in 85.8 per cent of the seven hearts studied.

Further, in the artery examined 18 months after implantation, not only was the artery open and branching, but it showed little intimal proliferation.

The clinical results in which 75 per cent of patients with coronary artery insufficiency were relieved of anginal pain after internal mammary artery implantation corresponds to the known mammary-coronary anastomotic rate in animals.

The cases mentioned were operated upon at the Royal Victoria Hospital, Montreal Institute of Cardiology, Jewish General Hospital and Queen Mary Veterans Hospital, Montreal, Canada.

RESUMEN

Se presentan evidencias de que la arteria mamaria interna implantada dentro del corazón humano isquémico como resultado de la enfermedad coronaria, permaneció abierta en su luz en el 85.8 por ciento de los siete corazones estudiados. Además, en la arteria examinada 18 meses después de la implantación no sólo estaba permeable y emitiendo ramas, sino que mostró pequeño proliferación de la íntima.

Los resultados clínicos en los que el 75 por ciento de los enfermos con insuficiencia coronaria se aliviaron del dolor anginoso después de la implantación de la arteria mamaria interna, corresponden a la proporción en que se sabe se obtienen la anastomosis mamario-coronaria en los animales.

RESUME

L'auteur démontre que l'artère mammaire interne implantée dans un coeur ischémié par une atteinte coronarienne resta perméable dans 85,8% sur les 7 cas étudiés. De plus, après 18 mois d'implantation, non seulement l'artère était perméable et implantée, mais elle montrait en outre une petite prolifération de l'intima.

Les résultats cliniques, dans lesquels 75% des malades atteints d'insuffisance coronarienne furent soulagés de leurs douleurs angineuses après implantation de l'artère mammaire, correspondent à la proportion connue des résultats de l'anastomose coronarienne-mammaire chez les animaux.

ZUSAMMENFASSUNG

Es wurde Beweismaterial vorgelegt, um zu zeigen, dass die art. mammar. int, wenn sie in das menschliche Herz implantiert wird, das ischaemisch ist infolge Coronar-Arterienerkrankung, in 85,8% der sieben überprüften Herzen offen blieb. Ausserdem waren die 18 Monate nach der Implantation untersuchten Arterien nicht nur durchgängig und verzweigt, sondern zeigten auch nur geringe Intima-Wucherungen.

Die klinischen Ergebnisse, wonach 75% der Patienten mit Coronar-Arterien-Insuffizienz von ihren anginösen Schmerzen befreit wurden nach Implantation der art. mammar, int., entsprechen der bekannten Mammaria-Coronarien-Anastomosenrate bei Tieren.

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Pulmonary Arteriovenous Fistulas of the Medial Basal Segment of the Right Lower Lobe: A Note on Absence of Vascular Bruits

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Classically, pulmonary arteriovenous fistulas are accompanied by vascular bruits. These are located over a segment or lobe of a lung and vary from a faint systolic sound often accentuated by deep inspiration to a loud harsh systolic blow. In a series of 16 cases with pulmonary arteriovenous fistulas studied at The New York Hospital,[1-3] all but two patients (both with fistulas of the medial basal segment of the right lower lobe) had characteristic bruits. The first patient with a pulmonary arteriovenous fistula of the medial basal segment of the right lower lobe, previously reported,[1] and the new case are herein recorded.

Study of the lobar and segmental divisions of the lung reveals that the medial basal segment of the right lower lobe lies deep within the thorax. Indeed, the "cardiac" segment is an alternate term. It is in contact with the heart along its mediastinal border; elsewhere, it is completely surrounded by other segments of the lung. Accordingly, an arteriovenous fistula in the medial segment of the right lower lobe appears to be silent. Because of the absence of a bruit, a high index of suspicion must be maintained. Careful scrutiny of the conventional chest roentgenogram should suggest the possibility of an arteriovenous fistula; angiocardiography will provide the definitive diagnosis.

Case Reports

Case 1: Pulmonary arteriovenous fistula, medial basal segment, right lower lobe, associated with rheumatic heart disease and hypertension. A 72 year old housewife (New York Hosp. No. 319819) was first admitted in 1946 because of blurred vision. A middle fossa meningioma was found, and removal of the tumor resulted in improvement of sight. During her stay evidences of mitral stenosis and insufficiency were elicited. In 1947 she returned because of epigastric cramps. Urologic study at that time disclosed cysts of the right kidney, which were removed. Chest x-ray film (Figure 1A) revealed nodular densities at the right base. The heart was enlarged, especially the right ventricle, pulmonary artery segment and left atrium. The blood pressure in 1946 was normal but in 1947 it had increased to 220/110 mm. Hg.

In 1949 cholelithiasis with obstructive jaundice developed which necessitated cholecystectomy and choledocholithotomy. Auricular flutter appeared prior to operation and was converted by digitalization to fibrillation. The post-operative period was stormy but the patient improved and was discharged. Subsequently she was seen periodically in the out-patient department. Early in 1951 central retinal artery thrombosis developed and she was readmitted to the hospital. This time the roentgen findings at the right base were suspected to be due to a pulmonary arteriovenous fistula; however, no bruit was heard and clubbing, polycythemia, and cyanosis of fingers and toes were not present. Angiocardiography (Figures 1B and C) was performed and an arteriovenous fistula of the medial basal segment of the right lower lobe was demonstrated. There was no history of familial bleeding and telangiectasia.

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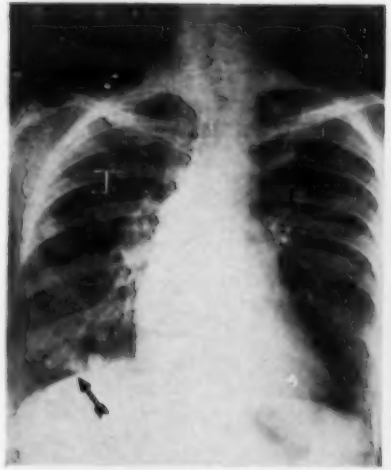

FIGURE 1A

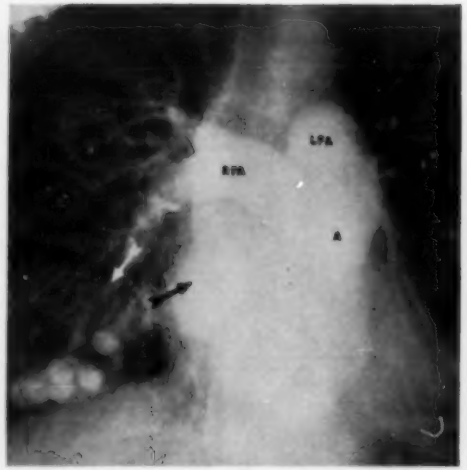

FIGURE 1B

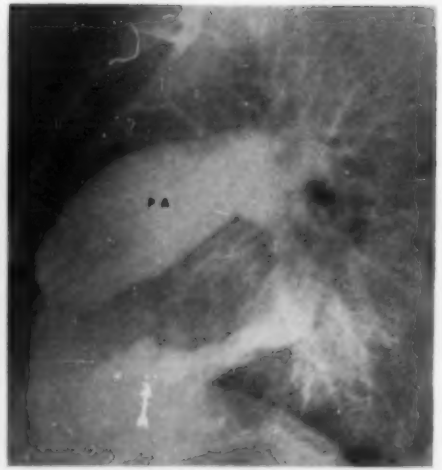

FIGURE 1C

Figure 1 (Case 1): A. Conventional chest roentgenogram showing a nest of small nodular densities just above the right diaphragm (arrow). The heart, pulmonary artery and branches are enlarged. B. Serial frontal angiocardiogram at five seconds shows a large pulmonary artery (PA) and branches (Right, RPA; left, LPA) due to mitral stenosis. A large segmental pulmonary artery from the right descending branch of the pulmonary artery (white arrow) proceeds to the right lower lobe connecting with a coiled series of rounded densities (arteriovenous fistula) which in turn empty via an efferent vein into the left atrium (black arrow). C. Left lateral angiocardiogram at three seconds shows the opacified main stem pulmonary artery (PA) and branches with an afferent segmental division connecting the circinate arteriovenous fistula of the medial basal segment, right lower lobe. (Republished with permission of Am. J. Med.[1]).

FIGURE 2A FIGURE 2B FIGURE 2C

Figure 2 (Case 2): A. Frontal teleoroentgenogram showing a cluster of small rounded densities near the right cardiac border (arrow). B. Lateral x-ray film shows the masses to be located in the medial basal segment of the right lower lobe (arrow). C. Frontal teleoangiocardiogram shows the opacified arteriovenous fistula (arrow).

The electrocardiogram showed right axis deviation, the rhythm varied between auricular flutter and fibrillation. She was last seen on October 17, 1956. She was totally blind and had become disoriented but polycythemia, clubbing and cyanosis of the fingers had not developed. Because of her poor general health and the symptomatic character of the pulmonary arteriovenous fistula, operation was not advised.

Case 2: Asymptomatic pulmonary arteriovenous fistula, medial basal segment of of the right lower lobe. A 64 year old housewife (New York Hosp. No. 684773) was admitted to the hospital for a minor gynecologic operation. A routine chest x-ray film disclosed an abnormal shadow at the right base. She denied respiratory complaints and there was no history of bleeding tendencies in the family. Physical examination revealed a well developed and nourished woman. The chest was clear, bruits were absent. There was no cyanosis or clubbing of the digits and telangiectases of the mucous membranes and skin were absent. The only abnormal findings were elevation of the blood pressure, 180/80 mm. Hg. and left axis deviation of the electrocardiogram. The chest x-ray films (Figures 2A and B) showed clusters of rounded densities with hilar vascular connections located in the medial basal segment of the right lower lobe. Blood studies were normal; the hematocrit was 43 per cent. Angiocardiography was done on August 2, 1956 (Figure 2C) and showed the classical appearance of a pulmonary arteriovenous fistula located in the medial segment of the right lower lobe. She was seen in the out-patient department during the past year. There were no respiratory complaints; however, hypertension persisted. Excision of the pulmonary arteriovenous fistula was advised but refused by the patient.

Comment

Figure 3, modified from Jackson and Huber's[4] and Boyden's[5-7] studies of the pulmonary segments clearly shows the medial basal (cardiac) segment of the right lower lobe to lie well within the thorax. Indeed, it is entirely surrounded by the neighboring segments save along its medial border; here it grooves the heart and is well away from the surface of the thorax (Figure 3B). This apparently explains the inability to elicit a bruit with the stethoscope. Whether a bruit might be heard with electrical magnification has not been ascertained. Since operation was not performed, it was not possible to determine whether a bruit would have been found in the exposed specimen. Boyden[6] rightly takes exception to the omission of a left medial basal segment in the international nomenclature. This segment, too, is adjacent to the heart. Since a pulmonary arteriovenous fistula has not been encountered in this area, it is not known if the bruit will also be absent.

Excision of a pulmonary arteriovenous fistula is recommended even in asymptomatic patients. This is because the incidence of cerebral abscess and thrombosis is high in this disease.[1, 2] In addition, fatal rupture of the paper-thin fistula has also occurred.[8] Even though a retinal thrombosis developed in Case 1, which may be related to the pulmonary arteriovenous fistula, the presence of rheumatic heart disease, hypertension, the advanced age, blindness and finally senility did not warrant operation. However, despite the age, it was recommended for the other patient (Case 2) but she declined surgery.

In both patients the frontal conventional roentgenogram showed a series of nodular densities at the right base adjacent to the right heart border (Figures 1A and 2A). Whether such an arrangement is characteristic of arteriovenous fistulas of the medial basal segment of the right lower lobe is unknown; since only two cases have been studied. Angiocardiography, however, established the diagnosis,[1, 2] despite the absence of a vascular bruit.

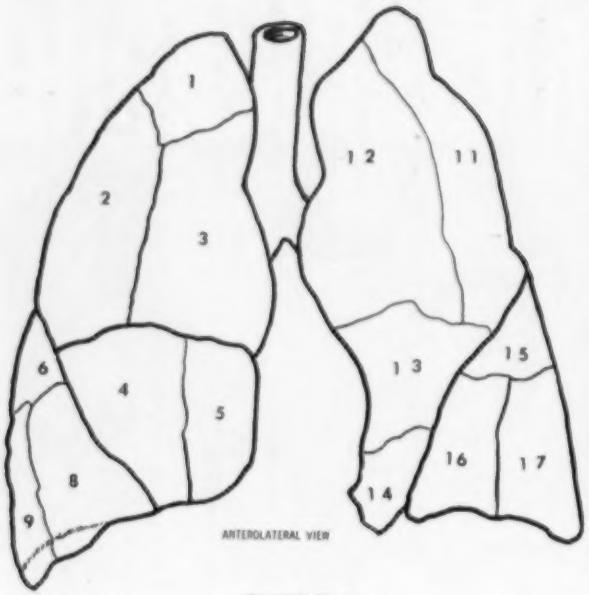

FIGURE 3A

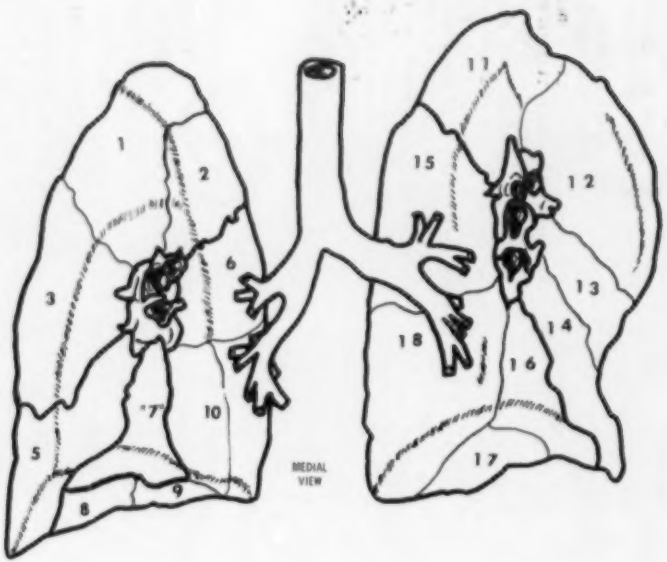

FIGURE 3B

Figure 3: The lobes and bronchopulmonary segments of the lungs. A. Anterolateral view. B. Mediastinal view. (Adapted from Jackson and Huber[4] and Boyden.[5, 6] Note that the medial basal segment of the right lower lobe "7" is located in the mediastinum and does not reach the surface of the chest wall.

Lobes of Left Lung—Upper Division of Upper Lobe: 11. Apical-posterior; 12. Anterior. Lower Division of Upper Lobe: 13. Superior; 14. Inferior. Lower Lobe: 15. Superior; 16. Anteromedial Basal; 17. Lateral Basal; 18. Posterior Basal.

Lobes of Right Lung—Upper Lobe: 1. Apical; 2. Posterior; 3. Anterior. Middle Lobe: 4. Lateral; 5. Medial. Lower Lobe: 6. Superior; 7. Medial Basal; 8. Anterior Basal; 9. Lateral Basal; 10. Posterior Basal.

SUMMARY AND CONCLUSIONS

Two elderly women were discovered, on routine roentgenography of the chest, to have a series of rounded densities with vascular hilar connections located in the medial basal segment of the right lower lobe. Despite the absence of a vascular bruit, angiocardiography was recommended and established the diagnosis of pulmonary arteriovenous fistulas.

Anatomic study of the pulmonary segments discloses that the medial basal (cardiac) segment of the right lower lobe lies deep within the thorax and that disease in this area is inaudible with the stethoscope. A series of rounded densities at the right base that appear to have vascular connections with the right hilus should arouse suspicion of being of vascular origin. Angiocardiography is recommended for diagnosis. If no contraindications exist, surgical excision even in elderly asymptomatic individuals is advised.

Acknowledgment: Thanks are due to Elissa Ettinger for preparation of Figure 3.

RESUMEN Y CONCLUCIONES

Al hacer roentgenfotografía a dos mujeres ancianas se descubrió que tenían una serie de manchas redondas con conexiones hiliares, ubicadas en el segmento medial basal del lóbulo inferior derecho. A pesar de la ausencia de ruido bascular se recomendó la angiocardiografía y se estableció el diagnóstico de fístulas pulmonares arteriovenosas.

El estudio anatómico de los segmentos deja ver que el medial basal (cardiaco) el lóbulo inferior derecho radica muy profundamente en el tórax y que los cambios en esta región son inauscultables con el estetoscopio. Una serie de manchas redondas densas en la base derecha, que parezcan tener anexos vasculares con el hilio derecho deben dspertar la sospcha de ser de origen vascular. Se recomienda la angiocardiografía para el diagnóstico.

Si no hay contraindicaciones la excisión quirúrgica se recomienda aún en personas ancianas asintomáticas.

RESUME

On a découvert à l'examen radiologique systématique du thorax chez deux vieilles femmes une série d'opacités arrondies siégeant dans le segment basal médian du lobe inférieur droit. Malgré l'absence de bruit vasculaire, une angiocardiographie fut conseillée, et elle permit de faire le diagnostic d'anévrysmes artérioveineux pulmonaires.

L'étude anatomique des segments pulmonaires infirme que le segment basal médian (segment cardiaque) du lobe inférieur droit s'étende profondément à l'intérieur du thorax, et qu'une atteinte de cette région soit inaudible au stéthoscope. Un groupe d'opacités arrondies de la base droite, qui semblent avoir des connections vasculaires avec le hile doivent faire soupçonner qu'elles sont d'origine vasculaire. L'angiocardiographie est conseillée pour affirmer le diagnostic. S'il n'existe aucune contre-indication, l'exérèse chirurgicale est recommandée même chez les individus âgés sans symptômes.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Es wurden 2 ältere Frauen bei planmässiger Röntgenuntersuchung des Brustkorbes entdeckt, die eine Reihe von abgerundeten Verdichtungen aufwiesen mit Gefässverbindungen zum Hilus und lokalisiert im medialem besalen Segment des rechten Unterlappens. Trotz des Fehlens von Gefässgeräuschen wurde zur Angiocardiografie geraten, und dies führte zur Feststellung der Diagnose von pulmonalen arteriovenösen Fistelm.

Die anatomische Untersuchung der pulmonalen Segmente enthüllte, dass das Mediale basale (cardiale) Segment des rechten Unterlappens tief im Thorax liegt und dass eine Erkrankung in diesem Bereich mit dem Stetoskop nicht hörbar ist. Eine Reihe von abgerundeten Verdichtungen an der rechten Basis, die Gefässverbindungen mit dem rechten Hilus zu haben scheint, sollte den Verdacht erwecken, vasculären Ursprunges zu sein. An giocardiografie zur Feststellung der Diagnose empfielt sich, Sofern keine Kontra-Indikationen vorliegen, ist chirurgische Excision selbst bei älteren Symptomenfreien Individuen ratsam.

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CURRENT THERAPY

With the addition of the Section on Cardiovascular Diseases, we are pleased to introduce a monthly series on current therapy in cardiovascular diseases. This is the first of this series and the Editorial Board invites comment from the readers of our journal.

Digitalis Therapy

Correct digitalis therapy can be considered an art and it has been said that a "life-time of experience" is necessary to master it.[5] Medical students can be taught only the general outlines of digitalis medication; the finer points are acquired only through experience. Certain well established rules exist for the beginning but it is not possible to predict how to proceed or when to stop; every course of digitalis therapy is a new experiment with an unpredictable outcome.

For most patients two or three tablets of 0.1 gm. of the powdered leaf U.S.P. daily will suffice to restore compensation or to slow the ventricles in the presence of atrial fibrillation although in rare instances of advanced heart failure it may be necessary to start with four or five such tablets daily. The end-point is reached when full compensation is restored or when signs of digitalis toxicity develop.

If congestive failure disappears in the course of atrial fibrillation with a rapid ventricular response one usually discontinues larger doses and administers a maintenance dose when the ventricular rate drops to 70 or 80. However, it is often necessary to give much more digitalis as in many cases of this kind the condition of the myocardium requires it.

Even in patients optimally digitalized the liver may remain enlarged, a right sided pleural effusion or ankle edema may persist. Increase in digitalis will not benefit these patients but on the contrary will lead to adverse effects such as general weakness and nausea.

The duration of digitalis therapy is variable. Some patients will require it for a life-time while others with myocardial infarction, pulmonary embolism, streptococcic or viral infections, or active rheumatic fever, may not need any medication once the cause responsible for the failure has disappeared or a strong fibrotic scar developed.

In recent years it has become common practice to replace this classical form of digitalis therapy which requires skill and knowledge by another more mechanical method. Without regard to the patient's age, weight, clinical condition or etiology of the cardiac failure, the "full dose" therapy is applied. The patient receives a calculated "average digitalizing" dose at once or in divided doses within 24 hours, the only disagreement being whether this dose should be 1.2 mg. of digitoxin or more. While the experienced clinician will deliberate whether to increase or decrease the daily dose by one tablet of 0.1 mg. knowing that this may spell the difference between well being and suffering, between digitalization without

or with side effects, with or without dangerous arrhythmias, others in the "modern way" try to accomplish digitalization rapidly and with large doses. Actually few patients encountered in hospitals and private practice must be digitalized rapidly. It may be a sign of our times that the quick full digitalization is so widespread and it may also be significant that with this haste the subjective feeling of the patient is often disregarded.

Particularly in elderly patients this method of rapid digitalization often leads to nausea and muscular weakness which may persist for weeks. Even more dangerous and not infrequent is the appearance of dangerous digitalis arrhythmias after as little as 0.6 mg. of digitoxin. On the other hand, some patients will require more than the above doses to obtain maximum benefits. This individualization of digitalis therapy can be compared to that of penicillin therapy for subacute bacterial endocarditis in which we can formulate only general rules at the onset of treatment; we have to modify them according to the clinical and laboratory findings.

Among the side effects the most dangerous are certainly the ventricular tachycardias often leading to ventricular fibrillation. Their danger lies particularly in the fact that they usually do not cause symptoms. They are often preceded by extrasystoles in bigeminal form. It is wrong to speak of them as a sign of digitalis intoxication since they are absent in healthy people even if lethal doses of digitalis are taken. Such extrasystoles appear in the healthy only in the last minutes of life or are completely absent. They appear only terminally in the healthy dog. On the other hand we have seen such extrasystoles particularly in patients with chronic mitral lesions in congestive heart failure even after administration of only 0.3 gm. of standard powdered leaf for one day. Some "abnormal state of the myocardium" is therefore a prerequisite for the appearance of these ectopic rhythms,[7] as we have pointed out for more than 30 years. The nature of this state was unknown until recently. It became clear in the past few years that the appearance of such extrasystoles is favored by a loss of potassium from the myocardial cell.[4] This loss of potassium is known to occur in chronic failure and also during administration of digitalis in large doses. It is impossible to predict when such extrasystoles will occur but they are always threatening. In using the classical method of digitalis therapy one will be able to stop in time when the first extrasystoles appear while with the full dose therapy the single extrasystoles increase in number, characteristic patterns of ventricular tachycardia appear and may be quickly followed by ventricular fibrillation and death. Only careful, continuous supervision and energetic action with the use of potassium chloride orally and quinidine intramuscularly may save some of these patients. When these extrasystoles appear in irregular groups they may on auscultation resemble the rhythm found in atrial fibrillation and therefore more digitalis is given with often fatal results. Digitalis extrasystoles originating in the ventricles show a characteristic continuous change of form. So do ventricular tachycardias. Atrial tachycardias show A-V block.

A-V heart block may also appear after administration of very small doses. Here too the intrinsic condition of the heart is partly responsible.

Ventricular extrasystoles and even ventricular tachycardias not caused by digitalis are no contraindication against the use of the drug. Actually digitalis usually brings about the disappearance of these arrhythmias. Even tachycardia with alternation of the form of the ventricular complexes disappears when digitalis is used.[6]

With regard to the question of rapid digitalization one must admit that most of the time the advantages for the patient are nil and the disadvantages great. Quick digitalization is necessary only under special circumstances: when atrial fibrillation with a fast ventricular rate and low blood pressure or congestive failure is discovered in a patient requiring an emergency operation, when a patient with coronary stenosis develops an atrial paroxysmal tachycardia or atrial fibrillation exists with continuous anginal pain or whether a patient with an acute myocardial infarction develops atrial tachycardia, atrial flutter or fibrillation.

It is known that sublethal doses of digitalis administered to animals cause focal necrosis in the myocardium and certain blood vessels. Such changes have not been reported in man. However, it is probable that although these histological changes that are seen only in severely damaged or dead cells are not demonstrable in man, large doses do lead to some harm to the muscle cells.

At the risk of being repetitious we would like to stress that digitalis therapy in every patient should be regarded as an individual problem. It is impossible to assume that every patient needs the same dose of digitalis for "full digitalization." If one formerly saw too many under-digitalized patients, at present many are over-digitalized and this must be considered a far greater danger. It is one thing to find out statistically what the "average digitalizing" dose is and another to treat every patient with this dose.

Another new aspect of digitalis therapy is the widespread preference for digitoxin. For many physicians it "has become a habit."[5] This is not a new preparation since digitoxin in the form of "digitaline Nativelle" has been isolated and widely used since 1869. Several claims have been made for its recommendation. One is that this preparation does not have to be controlled by bioassay methods. This is true of other isolated glycosides. Moreover, it was found that the potency of several digitoxins available at the present time is not identical; impurities occur which counteract the advantage of giving a "pure" preparation of digitoxin. Another advantage is said to be the complete absorption in the intestinal tract. This would be important if a certain amount of digitalis would always elicit the same response which as we have seen, is certainly not true. Furthermore, because of the different composition and absorption of other preparations of digitalis such as the standardized leaves from the beginning much larger doses are given.

A third claim often made is that digitoxin is a less toxic preparation. This is certainly not correct with regard to nausea, anorexia and even less

so with regard to toxic arrhythmias. The claim has also been made that digitoxin acts quicker than other digitalis preparations. This is also not a fact since digitoxin more than the other digitalis glycosides unites with blood proteins and therefore its action on the heart is slower. Preparations from digitalis lanata, such as digilanid C or digoxin work faster and, since their fixation to blood proteins is minimal, they dissipate faster.[1] Digitoxin on the other hand has the advantage of remaining fixed in the heart muscle longer and thus has a more extended action. It will be useful in the many patients needing continuous digitalis action for a prolonged period; however, tablets of standardized leaf contain digitoxin and therefore have the same effect.

It is of interest that digitalis powdered whole leaf tablets are not even stocked by some hospital pharmacies which instead dispense only the isolated glycosides. In one hospital a nurse with five years graduate experience did not know that powdered whole leaf tablets existed.

When quick action is needed such as during a paroxysmal tachycardia an intravenous injection of digilanid C, digoxin or strophanthin is useful. There is no point in injecting digitoxin in emergencies. The binding of the former substances to albumin in the blood being minimal they are of greater benefit to those patients who need only temporary digitalization or who because of the former appearance of extrasystoles require a drug which is more rapidly dissipated.

The statement has been made that digitalis must be given in larger doses when the heart is larger. This is not in accord with our experience and the largest hearts in valvular lesions, as seen in the combination of mitral and aortic lesions with a tricuspid insufficiency need often very small doses of digitalis for maintenance of full compensation. Patients with coronary sclerosis and heart failure need larger doses even if the heart is scarcely enlarged.

It seems that with rapid digitalization and too rapid diuresis thromboembolic phenomena occur more often than when one proceeds in a conservative manner.[3] The weight of the patient should be considered when the dosage of digitalis is evaluated. An analysis and explanation of this and other observations mentioned below will not be possible as long as we do not know how digitalis acts, whether on the muscle proteins or on the enzymes, whether it accelerates dephosphorilization or acts on adenosine triphosphate.

It is well known that under certain conditions digitalis does not improve the failing heart. A typical and unfortunately common example of this observation is cardiac failure in patients with active rheumatic carditis where sometimes cortisone brings about quicker improvement than digitalis does. If one finds in patients with atrial fibrillation that the ventricular rate remains rapid in spite of administration of large doses of digitalis it will often be observed that one of the following situations prevails. A widespread active carditis in rheumatic valvular lesions may be present without other clinical manifestations, particularly, with a normal sedimentation rate. Another condition that may be present is a pulmonary

embolism which for unknown reasons makes it impossible to slow the ventricles in the presence of atrial fibrillation. A third condition is masked hyperthyroidism which responds quickly to specific treatment. It should be emphasized here that in many forms of sinus tachycardia digitalis does not slow the heart rate. Even with atrial fibrillation, instances are known where the ventricular rate remained unchanged after administration of 2 mgm. of digitoxin within 24 hours.

During digitalis therapy diuretics are often given and their use may lead to the phenomenon of re-digitalization. The most common effect of this is the appearance of extrasystoles often in form of coupled beats for a few days following a profuse diuresis due to a mercurial diuretic. This effect was originally attributed to the absorption and re-circulation of digitalis from the edematous fluids and the transudates. These fluids were supposed to contain relatively large amounts of digitalis. More recently this has been denied and it has been claimed that the loss of potassium through profuse diuresis is the cause of the extrasystoles. This may well be true but we cannot accept it as the exclusive explanation since louder and more forceful heart sounds or the disappearance of a gallop rhythm indicate improvement in the state of the myocardium. As long as this cannot also be attributed to loss of potassium we will keep the old explanation in mind.

Strophanthin therapy is used too seldom. Many reject it without ever having tried it, while others have thought it useless or weak. It must be remembered that strophanthin although kept under sterile condition will deteriorate rapidly if the glass container or ampoule does not meet certain specifications concerning its content of potassium. Still others do not use it because they observed fatal accidents shortly after the injection. In such cases inquiry will reveal that the dose given was 0.5 mg. which is unfortunately still recommended widely in books and articles. Actually the single dose should rarely exceed 0.25 mg. and should be even less in the patient who has had digitalis in recent weeks or who has responded to former attempts at digitalization with the appearance of extrasystoles. An increasing number of extrasystoles and ventricular fibrillation are the only real dangers of strophanthin therapy and this danger can be avoided with the use of smaller doses and observation of the patient for 30 minutes following each injection. If no extrasystoles appear the dose can be repeated safely the next day. The slowing action on the ventricle in the course of atrial fibrillation is not as pronounced as with digitalis. There is no doubt, however, that preparations such as ouabaine and strophosid do work quicker and often with much less side-effects in patients with myocardial fibrosis, myocardial infarction and heart failure than any other preparation. Strophanthin is dissipated quickly and the injection must be repeated every 24 to 48 hours. The disadvantage of chronic therapy is the necessity for an intravenous injection, since oral or rectal administrations are, for all practical purposes, ineffective; for initiation of a digitalis effect however strophanthin is unsurpassed if speed is essential. It is often dogmatically stated that three days should elapse between the ad-

ministration of the last dose of digitalis and the first dose of strophanthin. The duration of this interval depends on many factors among which is the response of the patient to digitalis and the type of digitalis used, i.e., whether a long acting cumulative digitalis preparation such as digitoxin or a rapidly dissipated one like digoxin has been given. The use of the recently introduced actyl strophantidine is not without risk because of its fast action.

In recent years gitalin preparations have again been recommended. We used them 30 years ago as Verodigen and found them to be reliable, effective preparations particularly in the form of suppositories. In general there is no remarkable advantage derived from the use of this preparation and the statement is still correct that it does not matter much which type of digitalis preparation is used but how it is used.

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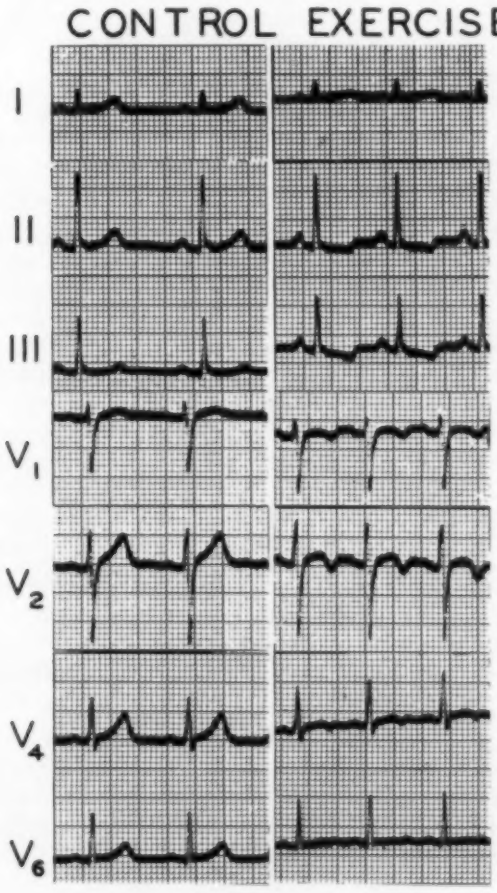
THE ELECTROCARDIOGRAM OF THE MONTH

This "Electrocardiogram Of The Month" is the beginning of a series. The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

Electrocardiograms A and B were made, respectively, before and after exercise employing a bicycle exerciser. The 26 year old subject has no symptoms and no signs of heart disease. His blood pressure is 120/80. There are no evidences of arteriosclerosis in the peripheral vessels or the eyegrounds. He is not a diabetic. He is apparently in good health.

Explanation

The subject is a healthy intern at the Touro Infirmary who was used as a subject for a controlled study of the effect of exercise upon the electrocardiogram.



The inversion of the T waves in Lead II and III and in the precordial leads is commonly observed with rapid rate, after 20 rapid deep knee bends, or after a period of bicycle exercise sufficient to cause dyspnea. The inversion of the T waves in the middle and right precordial leads is more unusual as a purely exercise effect. However, it is commonly observed after hyperpnea and in this instance it is also due to the fact that the mean T effects are made to point upward (away from all of the chest electrodes) when the exercise causes a marked diminution in the magnitude of the ventricular gradient.

Less exertion produces similar effects if performed 30 minutes to an hour after a meal. Smoking has a marked effect in some persons. Many errors in diagnosis result from the prevalent deep-rooted prejudice against inverted T waves in lead II and in the left precordial leads. These are commonly interpreted as abnormal regardless of the circumstances under which they are observed. It seems clear to us that in many instances the proper evaluation of low or inverted T waves can only be made by studying tracings made 1) under basal conditions, 2) after exercise, 3) after a meal, 4) after exercise performed 45 minutes following a meal. The series of observations should be made on the same morning. In some cases the effects of other factors should be observed (e. g., smoking).

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Carcinoma in Collagen Disease

With an Illustrative Case Report

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The association of carcinomatous changes with lupus erythematosus of the skin has been recognised since 1886, when the first cases were described by Riessmeyer and also by Curie. In 1934 Uhlmann and Schambye[1] were able to collect 107 cases from the literature. Kappesser[2] analysed 140 cases in 1952 and calculated a maximal incidence of carcinomatous change of one in every 52 cases of lupus erythematosus of the skin. He found 81 of 87 of the tumours to be squamous cell carcinomas, four were basal-cell carcinomas and two were mixed-cell types. Schwarz[3] (1953) found the incidence in the patients attending his clinic to be one in 213. Köpf[4] demonstrated the first spindle-celled fibrosarcoma in such skin lesions in 1946 and Grasreiner and Sterba[5] published a further spindle-celled fibrosarcoma in 1954. Tar carcinoma of a lupus erythematosus scar has been described by Rosmanith.[6]

Whether a specific etiologic relationship exists between these skin lesions and the malignant changes is controversial. Schwarz[3] has outlined three possibilities: (a) the conjunction of the two conditions may be accidental; (b) the treatment of the lupus lesions by irritants such as caustics or irradiation, promotes the development of malignant change; (c) there is a specific predisposition to malignant change in the skin lesions of lupus erythematosus. In his series 10 per cent were previously untreated, and he concluded that the predisposition was not specific, but similar to that found with lupus vulgaris, burn scars, radiation damage, chronic light sensitivity, and other conditions in which skin atrophy occurs. In Montgomery's[7] experience there was a lower incidence of epitheliomatous change in lupus erythematosus than in lupus vulgaris.

Whatever the ultimate conclusion about this relationship, there is no doubt that carcinomatous change is frequent in lupus erythematosus of the skin. We have not, however, been able to find a reference in any of the major publications on the subject to carcinomatous change occurring in other organs affected by the visceral changes of systemic lupus erythematosus.

The association of malignant disease with other collagen diseases has been repeatedly noted in dermatomyositis. The first description of visceral changes in this disease by Urbach[8] in 1930 was soon followed by Bezecny's[9] report of three cases with associated carcinoma of the ovary or breast.

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Sheard and Knoepfler[10] were able to collect 70 cases associated with malignant disease by 1956, the predominant site of the malignant change being in the gastro-intestinal or genital tract. Cases associated with carcinoma of the lung have been frequently described.[11-14] Schuermann[15] contrasted the situation with that in scleroderma, also a collagen disease, and one sometimes difficult to differentiate from dermatomyositis. In his study of 600 cases of scleroderma over 20 years he failed to find a single instance of associated malignancy. Zatuchni et al[16] were to describe the first such cases in 1953. In each of their three cases an unsuspected terminal bronchiolar ("Alveolar-cell") carcinoma was found in association with the pulmonary fibrosis of scleroderma. In addition they reported three other malignant lesions in a series of 39 patients with scleroderma, two being carcinomas of the breast in women and one an undifferentiated widely disseminated fibrosarcoma in a man. Jonsson and Houser[17] have since added a case of bronchogenic adenocarcinoma in a woman with scleroderma. Carcinoma of the lung has also been described in conjunction with widely ranging conditions apart from the collagen diseases, and in asbestosis an etiologic relationship is believed to exist.

The close association between dermatomyositis and visceral tumours has given rise to several etiological conceptions. Brunner and Lobraico[18] and Curtis et al[19] have suggested that the cutaneous lesions are the result of sensitisation to the products of the tumour or its destruction. Becker et al[20] postulate a minimal metastic infiltration of skin and muscle, with a resulting inflammatory mesenchymal reaction and destruction of the neoplastic cells. Various authors have reported amelioration of symptoms of dermatomyositis coincidental with effective treatment of the malignant tumour.[19, 20] Bezecny[9] reported improvement in skin and muscle manifestations after excision of the primary tumour in three cases, to be followed in one by recurrence at the appearance of metastases. Similar experiences have been reported by Dostrovsky et al.[11]

Carcinoma of the lung is the commonest of all neoplasms to give rise to remote manifestations not due to obvious metastases. Syndromes suggestive of rheumatoid disease have been described, with joint pains and the development of chronic arthritis sometimes leading to the complete picture of hypertrophic pulmonary osteoarthropathy. In addition neurological disturbances have recently been reported which include primary sensory neuropathy, mixed motor and sensory polyneuritis, acute cortical cerebellar degeneration and various myopathies such as are found with dermatomyositis. These various complications often precede other signs of the tumour by long intervals. Curtis et al[19] in eight cases of dermatomyositis, found the latent period to be on an average of 18.6 months. Miller[21] in a review of the subject, discusses some of the possible ways in which such complications could arise, concluding that they may represent a sensitisation reaction to some antigenic product of the growth. In serum sickness, a frankly allergic disorder, radicular and peripheral neuropathies are well known.

There is thus mounting evidence that a variety of conditions ranging

from dermatomyositis to peripheral neuritis and myopathies can be associated with carcinoma of the lung. These manifestations frequently precede the clinical appearance of the neoplasm, and generally improve if not disappear, with its successful extirpation. It seems likely that in such cases the relationship is an etiological one, and that some product of the tumour is the intermediary, effective either directly on the tissue involved, or acting through a process of sensitisation.

We here present a case in which systemic lupus erythematosus was found associated with an oat cell bronchial carcinoma. These conditions have not, apparently, been previously described together, and their possible relationship is discussed.

FIG. 1

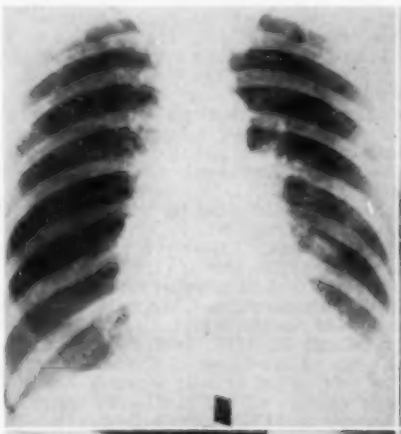

FIG. 2

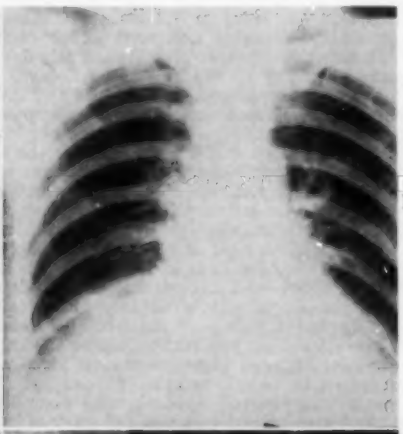

FIG. 3

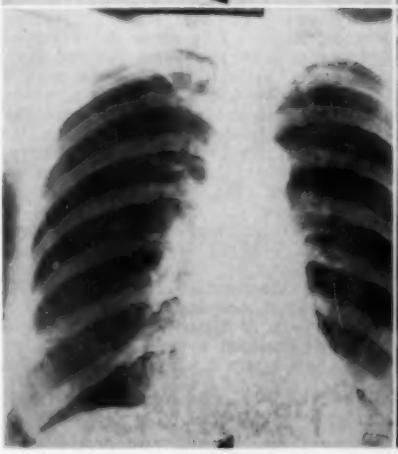

FIG. 4

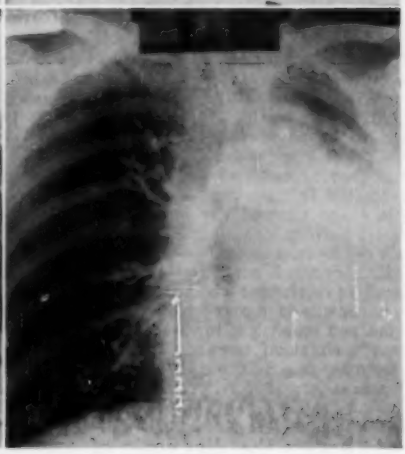

Figure 1: Hospital admission film showing small area of mottling left midzone.—*Figure 2:* Some collapse of right middle and lower lobes, and also left lower lobe. Pleural changes present.—*Figure 3:* Right lung clear. Tight collapse of left lower lobe (due to carcinoma) concealed behind heart shadow.—*Figure 4:* Bronchogram showing collapse of whole left lung, with almost complete obstruction of left main bronchus.

Case Report

A woman aged 49 first attended as an outpatient in January 1955 with a history of a persistent cough, wheezing and a small amount of sputum for many years. On three occasions, towards the end of 1954, there had been small amounts of blood in the sputum at the time of severe bouts of coughing.

She had had a mild attack of rheumatic fever at 17 years of age and two episodes of left-sided pleurisy in 1930 with "congestion of the lung" in 1935. She had smoked 20 to 30 cigarettes a day all her adult life.

On examination there was no abnormal physical sign and a chest radiograph showed the lungs to be clear. As she had been working in a factory for the previous 10 weeks where much ammonia was used, her symptoms were attributed to the aggravation of a long-standing bronchitis by the ammonia fumes.

After giving up this work she remained well until April 1955, when she suddenly became extremely ill, with a high fever, dyspnoea and blood-stained sputum. On admission to hospital generalised rhonchi and rales were heard anteriorly in the left upper and mid-zones of the chest. The initial chest radiograph (Figure 1) showed only a small area of mottling in the left mid-zone, which did not seem sufficient to account for the severity of her condition, but Haemophilus influenzae and Staphylococcus aureus were grown from the sputum. White cell counts ranged between 5,500 and 6,300 per cubic mm. with about 70 per cent neutrophils. Treatment, first with penicillin (½ a mega. unit twice daily for four days) and then tetracyclin (250 milligrammes every six hours for four days) had no effect on her condition, and during this time physical signs of collapse and consolidation of the right lower lobe appeared. This was confirmed by further radiographs (Figure 2) which also showed some collapse to be present in the left lower zone. Chloromycetin (500 milligrammes every six hours) was then given and with this the infection was brought under control. During this time a soft apical systolic murmur was occasionally heard. She was discharged May 12, 1955 and when seen as an outpatient May 24, 1955 was symptom free. A radiograph showed the right side to have cleared completely, but there was still a slight amount of inflammatory change in the left lower zone.

She remained well until the beginning of July, when a butterfly erythematous rash developed over her nose and cheeks, with the typical appearance of lupus erythematosus. The rash extended around her mouth, down her neck and affected her hands. About this time cough with a slightly blood-stained sputum returned. She also complained of pain and swelling of the left knee, and marked tenderness over the anterior ends of her ribs. She was readmitted to the hospital July 20, 1955. In addition to the rash and joint changes there were now physical signs of a collapse of the left lower lobe, confirmed by a radiograph (Figure 3). The soft apical systolic murmur heard previously reappeared. Albumin and a moderate number of red blood cells were found in the urine. Blood examination showed a leucopenia (4,650 white cells per cmm. with 60 per cent neutrophils). A diagnosis of acute systemic lupus erythematosus was made, although bone marrow examination on two occasions failed to show the presence of L. E. cells. Treatment with ACTH (80 milligrammes a day) was started and resulted in marked improvement in the rash and joint pains. At this time it was considered that the lesion in the left lung was due to lupus erythematosus and it was hoped to confirm this by histological examination of a bronchoscopic biopsy. This investigation had to be postponed however, because the rash had extended around her mouth and made her lips inflamed and tender. While waiting for this to improve, bronchography was carried out and showed that the collapse had now involved the whole of the left lung, the left main bronchus being completely occluded (Figure 4). Bronchoscopy at this stage showed the lumen of the left main bronchus, just below the carina, to be obstructed by granular swelling. A biopsy showed the histological appearances of oat cell carcinoma.

Her general condition precluded any surgical treatment, there being evidence of renal involvement with urinary symptoms and red blood cells in her urine. ACTH was continued and seemed to keep the lupus erythematosus under control. The rash remained much less marked and although red blood cells persisted in her urine, a blood urea estimation towards the end of the illness was within normal limits (24 milligrammes per 100 milliliters). Nevertheless she gradually became weaker and died December 1, 1955. Post-mortem examination was refused.

Discussion

Although the diagnosis of systemic lupus erythematosus could not be confirmed by the finding of L. E. cells in this case, many of the characteristic features of the disease were present. At least eight of the 10 criteria laid down by Jessar et al[22] were fulfilled. The butterfly rash, acute migratory polyarthritis, changing cardiac murmurs, varying overt and micro-

scopic haematuria, albuminuria, pulmonary signs apart from those attributable to the carcinoma, anaemia, and persistent leucopenia despite acute pulmonary infection, all indicated a severe systemic disorder clinically in keeping with systemic lupus erythematosus. The response to ACTH with recrudescence of rash and polyarthritis when dosage was reduced was also in favour of this diagnosis.

During the patient's two hospital admissions the pulmonary manifestations of left-sided pneumonia followed by right-sided lower lobe collapse, which both cleared, only to be succeeded at an interval by left lower lobe collapse, are in keeping with the description by Gould and Davies[23] of the radiological findings in their large series. Harvey et al[24] in a clinical analysis of 138 cases found pleural involvement one of the hallmarks of systemic lupus erythematosus and also described persistent pulmonary consolidations lasting up to eight months, with chronic interstitial pneumonitis leading to atelectasis and respiratory failure. Lung changes were found in 46 of 105 patients. Twenty had changes considered to be produced by the lupus, six had pulmonary tuberculosis, five lobar pneumonia, two lung abscess, nine lobular pneumonia, two aspiration pneumonia and one repeated haemoptyses. The last is of interest in view of the presenting symptoms in our case.

In retrospect it seems likely that these presenting symptoms, of cough and haemoptysis, were due to the carcinoma of the left main bronchus, which had not reached a size sufficient to produce radiological abnormality. The distinctive features of the lupus subsequently masked those of the neoplasm. Similar problems arose in the case reported by Williams and Lundberg,[25] where there was the association of systemic lupus erythematosus, a meningioma and carcinoma of the cervix. Here the neurological signs and symptoms, at first attributed to the lupus, only cleared after the diagnosis and successful removal of the meningioma.

It is tempting in our case to relate the lupus to the carcinoma, and postulate that, as in skin lupus, the lesions in the bronchial mucosa were potentially malignant, the carcinoma being precipitated by the irritant effects of heavy smoking and later exposure to ammonia fumes; or to suggest that a primary bronchial neoplasm gave rise to the clinical picture of systemic lupus erythematosus through some mechanism of tissue sensitisation. In the case described by Jonsson and Houser,[17] in which there was a 10 year history of scleroderma, the diffuse interstitial lung fibrosis was thought to be the likely cause of the carcinoma. In ours the relationship may have been accidental, and this is supported by the fact that no other case has apparently been previously described. However, the association of scleroderma with malignant disease had not been found, although sought for, until 1953,[16] since when seven cases have been reported. It may be that carcinoma will prove to be as frequent an occurrence in lupus erythematosus as in other collagen diseases.

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Editorial

The Contribution of the International Congresses on Diseases of the Chest to International Understanding

Walter Pater wrote that a concentration of interest is precedent to the finest flowering of the arts, sciences, philosophies, and life itself. This explains the basis of the great contribution to international understanding and friendship made by Congresses of the American College of Chest Physicians; they are built around a concentration of interest—specialism in diseases of the heart and lungs.

Specialisms in crafts and professions are the hallmark of a highly-developed and integrated community. They are not something new. Herodotus described them in Egyptian medicine of 4,500 years ago. For their beginnings there are two outstanding reasons: Public demand, to fulfill a social need of the times, and the inherent desire in some men to do one or two things efficiently rather than many things adequately. For their growth to fruition on correct lines one thing is especially necessary: An interchange of viewpoints in frank discussion.

The field of research has made such enormous advances in theory, technique and apparatus that it is now beyond the scope of one man to attain full efficiency in more than one branch of medicine. Moreover it is rare for one opinion to be enough; the specialist in diseases of the chest requires the support and checking of one or more scientific investigators, with their laboratory tests, radiography and electrical readings, and often such collaborators must be called in at regular intervals in order to assess the value of treatment or the prognosis of the illness. That is why the College embraces so many allied specialisms.

The chest specialist cannot afford to let up on his reading if he is to retain his own self-respect, and to have the highest of all prizes in the respect of his colleagues. He must know what his fellow-specialists are doing in countries outside his own; better still he must try to meet them, know them, and correspond with them.

International conferences help us to acquire the art as well as the science of our specialism; listening to learned papers is not the whole story. Graphs and statistics can give broad indications on treatments and their results, but patients often beat mathematical prognosis and refuse to fall into neat categories. The real value of our conferences comes out in panel discussions, and in those intimate sharings of experience that result from the social programmes, when we "talk shop." It is then we learn that the personal factors that explain reactions to illness are universal; that in dealing with our own patients we are dealing with citizens of the world.

Above all, we make lasting friendships. Every International Congress results in growing correspondence with fellow-members, from Athens to Oslo, Johannesburg to New York, Taiwan to London. A member of the College is not an Indian or a Californian or a Scotsman; he is a colleague in a medical fellowship. To meet him anywhere is to meet a friend; to be at war with him is unthinkable.

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*Regent for England.

The President's Page

A New Year has just begun and there are many College activities to which we may look forward—the 24th Annual Meeting to be held in San Francisco this spring, the Fifth International Congress in Tokyo, September 7-11, and many chapter and regional meetings.

The Interim Session of the College held in Philadelphia last month, was a tremendous success. The Scientific Program, prepared under the chairmanship of Dr. Robert V. Cohen, drew a record attendance of over four hundred members and guests. I would like to congratulate Dr. Cohen and his committee on the fine program, and thank the officers and members of the Pennsylvania Chapter of the College for their splendid hospitality.

Plans for our Annual Meeting and for our next International Congress are progressing satisfactorily, and I trust that many of the members of the College are planning to attend these two important sessions.

I would like to make a *very important* announcement regarding the 24th Annual Meeting of the College to be held at the Fairmont Hotel in San Francisco, June 18-22. Most of you are aware of the acute hotel situation in San Francisco, and in order to be assured of satisfactory hotel accommodations during our Annual meeting, it is essential that you follow the proper procedure. If you are planning to attend the College meeting *only*, and not stay over in San Francisco for the Meeting of the American Medical Association, complete the coupon on page xxiii, and send it *at once* to the San Francisco Convention and Tourist Bureau, via air mail, with the required deposit. If you plan to remain in San Francisco for all or a portion of the American Medical Association meeting June 23-27, it is *essential* that you attach to the College coupon a completed hotel reservation form clipped from an issue of the Journal of the American Medical Association. Applications for reservations will be accepted by the Convention Bureau in the order in which they are received and only by following this procedure can you be assured of remaining in the same hotel for both the College and the American Medical Association meetings. I have been informed that the first hotel reservation coupon will appear in the January 4th issue of the *Journal of the American Medical Association*, and I cannot stress too strongly the importance of sending in the coupons at once. Unfortunately San Francisco does not have a sufficient number of rooms in the larger hotels to accommodate every physician who plans to attend the meetings. There are, however, many excellent accommodations in the smaller hotels and the new tourist courts are recommended by the Convention Bureau.

The Board of Regents of the College adopted a resolution at the Interim Session in Philadelphia to expand the College committees so that our members in all countries will have an opportunity to participate in committee activities. The international committees will meet at the time of our international congresses to discuss their programs and present reports. Plans are now being put into effect to organize these committees so they will be able to meet in Tokyo.

The Board of Regents accepted an invitation from the Honorable Edwin L. Mechem, Governor of the State of New Mexico, to hold a homecoming meeting of the College in his state in 1959. During that year the College will celebrate its Silver Anniversary and a number of special events will be arranged. The College held its first meeting in Albuquerque in 1935 and it is appropriate that we return to celebrate our Twenty-Fifth Anniversary. The City of Albuquerque has pledged its support to the College in this homecoming celebration. The meeting in Albuquerque is planned for the fall and will be held in addition to the 25th Annual Meeting of the College scheduled for June 3-7, 1959 in Atlantic City. Dr. J. Arthur Myers is preparing a history of the College for our Twenty-Fifth Anniversary. A special feature of the history will include photographs of fathers and sons who are members of the College. If any of our father-and-son members have not sent their photographs to the Executive Offices in Chicago, they should do so without delay.

Mrs. Gordon joins me in sending you and your families our very best wishes for the New Year.

Burgess L. Gordon

PROGRESS REPORT ON TOKYO CONGRESS

Plans for the Fifth International Congress on Diseases of the Chest to be held in Tokyo, Japan, September 7-11, 1958, are well under way. Murray Kornfeld, Executive Director of the College, spent several weeks in Japan meeting with College officials in that country and with members of the Japan Chapter. A meeting of the chapter was held at Chinzanso, Tokyo on October 9, 1957. The meeting was attended by a large number of College members in Japan (see photograph), at which time plans for the Congress were reviewed and discussed. It was decided to hold the scientific sessions of the Congress in the Dai-Ichi Building which has two theaters seating 700 and 300 respectively. A separate room will be used for the continuous showing of motion pictures during the Congress. The secretariat of the Congress will also be established in the Dai-Ichi Building.

The Inaugural Session of the Congress will take place in the Yomiuri hall, and the closing banquet will be held at the Tokyo Kaikan. All of the above-mentioned facilities are in the center of the city and within easy walking distance from the hotels.

Arrangements are also being completed for technical and commercial exhibits.

The Imperial Hotel in Tokyo has been selected as the headquarters hotel to house the delegates and other first class hotels in Tokyo have been engaged for the Congress.

PRIME MINISTER OF JAPAN ACCEPTS HONORARY PRESIDENCY

Left to right: Prof. Jo Ono, Prof. Yoneji Miyagawa, Murray Kornfeld, Prime Minister Nobosuke Kishi, Prof. Taizo Kumagai, and Prof. Arao Imamura.

The Honorable Nobusuke Kishi, Prime Minister of Japan, agreed to serve as the Honorary President of the Fifth International Congress on Diseases of the Chest in Tokyo next September. A number of important officials in the Japanese government will be invited to serve with the Prime Minister as honorary members. All of the ambassadors residing in Tokyo will also be invited to serve as honorary members of the Diplomatic Committee.

Meeting of Japanese Chapter

Front row, left to right: Prof. Jiro Ishida, Tokyo District Chairman; Prof. Naotsugu Kawai, Chairman, Scientific Assembly; Prof. Masanaka Terada, Chairman of General Affairs; Prof. Yoneji Miyagawa, Vice President of the Congress; Prof. Taizo Kumagai, President of the Congress; Prof. Arao Imamura, President, Japan Chapter; Mr. Murray Kornfeld, Executive Director of the College; Prof. Jo Ono, Secretary General of the Congress and Regent for Japan; Prof. Hidejiro Haruki, Governor for Japan; Prof. Osamu Kitamoto, Chairman, Scientific Program; and Captain Ralph Volk, Chief of Medicine, U. S. Naval Hospital, Yokosuka.

OFFICERS AND COMMITTEES

The College has 132 members in Japan and every member is being assigned to serve on one of the many committees in order to facilitate the organization of the Congress. The President of the Congress is Professor Taizo Kumagai of Sendai University. The Vice Presidents are: Professors Hiroshige Shiota, Yoneji Miyagawa, Seizo Katsunuma, Arao Imamura, and Yas Kuno. Members of the Executive Committee are: Professors Masanaka Terada, Osamu Kitamoto, Masao Tsuzuki, and Naotsugu Kawai. Mr. Taizo Ishizaka, President of the Federation of Economic Organizations, one of the leading industrialists of Japan, is Chairman of the Committee on Finance. He is being assisted by Mr. Ichiro Yano, President of the Dai-Ichi Mutual Life Insurance Company. Professor Jo Ono, Regent of the College for Japan, is Secretary-General of the Congress.

SCIENTIFIC PROGRAM

Scientific papers, panel discussions, fireside conferences and motion pictures will be presented on the following subjects:

Cardiopulmonary Function Studies	Aviation Medicine
Tuberculosis	X-Ray Radiation
Coronary Disease	Cardiopulmonary Pediatrics
Benign and Malignant Tumors	Occupational Diseases of the Chest
Cardiovascular Surgery	Asthma and Emphysema
Bronchoesophagology	Miscellaneous Topics

Eminent scientists from countries throughout the world will participate in the discussions, which will be simultaneously interpreted into the three official languages of the Congress, i.e., Japanese, French and English. There will also be scientific and commercial exhibits and visits to various medical institutions and hospitals in Japan.

SOCIAL PROGRAM

An interesting program of social activities is being planned by the committee in Japan which will include official receptions, tea ceremonies served by Geisha girls, a Japanese kimono fashion show, flower arrangements, a Japanese musical, and special Japanese dining including tempura, Ghengis Khan, sukiyaki, etc. In addition, there will be tours arranged to view Mount Fuji, Shrines, Buddhas, Japanese gardens and parks, as well as other places of interest.

POST-CONVENTION MEETINGS AND TOURS

Following the close of the Congress in Tokyo, a group of physicians will leave for Kyoto to participate in the 7th International Congress of Bronchoesophagology sponsored by the International Bronchoesophagological Society. Dr. Chevalier L. Jackson, Philadelphia, serves as secretary of this society. In addition to the scientific program, plans are being perfected for a social program, as well as sight-seeing in and around Kyoto.

A side-trip to Nara, one of the national parks of Japan, will be arranged. The group will then proceed to Hakone where a limited number of rooms will be available at the Fuji Hotel. Hakone is one of the famous spas of Japan and is situated in one of the most beautiful mountain resort areas in the country. The group will then proceed via air to Hong Kong.

The programs which are being arranged by the College chapters in Hong Kong and the other countries to be visited at the close of the Congress in Japan will be covered in future issues of *Diseases of the Chest*.

For those planning to participate in the Grand-Congress Tour, it should be pointed out that the number will be limited to the first class accommodations and air transportation available. It is requested that they file their applications as soon as possible with the Executive Director of the College in Chicago.

INTERIM SESSION

The Interim Session of the College held at the Warwick Hotel, Philadelphia, on December 2 and 3, was one of the most successful and best attended fall meetings the College has ever had. More than four hundred members and guests were present for the scientific session presented on Monday, December 2, and the cocktail party and dinner that followed were attended by the maximum number of persons the hotel could accommodate. The Pennsylvania

Chapter of the College was host at the cocktail party. Dr. Burgess L. Gordon, President of the College, presided at the dinner and introduced the officials and guests. Mr. Robert K. Bell, Ocean City, New Jersey, Past President of the New Jersey State Bar Association and member of the House of Delegates of the American Bar Association, was guest speaker and gave a very interesting talk on "The Challenge to the Medical and Legal Professions." The evening closed with a series of Fireside Conferences on a variety of subjects of special interest to heart and lung specialists.

On Tuesday, December 3, the Executive Council, Board of Regents and Board of Governors held their semi-annual meetings, and a number of councils and committees of the College held special meetings during the day. The proceedings of the administrative meetings follow.

ADMINISTRATIVE SESSIONS
Warwick Hotel, Philadelphia
December 3, 1957

The following Regents, Governors, Chapter Officers and Council and Committee Chairmen attended the sessions of the College in Philadelphia:

Osler A. Abbott, Atlanta, Georgia
Albert H. Andrews, Chicago, Illinois
Alvan L. Barach, New York City
Gerald Beatty, Wilmington, Delaware
Samuel Bellet, Philadelphia, Pennsylvania
Otto L. Bettag, Chicago, Illinois
Katharine R. Boucot, Philadelphia, Pennsylvania
Otto C. Brantigan, Baltimore, Maryland
Charles A. Brasher, Mount Vernon, Missouri
John F. Briggs, St. Paul, Minnesota
Ross K. Childerhose, Harrisburg, Pennsylvania
Robert V. Cohen, Philadelphia, Pennsylvania
Sumner S. Cohen, Oak Terrace, Minnesota
Dean B. Cole, Richmond, Virginia
James P. Cooney (Maj. Gen.), Washington, D. C.
Edgar W. Davis, Washington, D. C.
Everett C. Drash, Charlottesville, Virginia
Seymour M. Farber, San Francisco, California
M. Jay Flipse, Miami, Florida
Carl H. Gellenthien, Valmora, New Mexico
Roy F. Goddard, Albuquerque, New Mexico
Alfred Goldman, Los Angeles, California
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Albuquerque, New Mexico
Edward A. Greco, Portland, Maine
J. E. J. Harris, Albuquerque, New Mexico
Chevalier L. Jackson, Philadelphia, Pennsylvania
Hollis E. Johnson, Nashville, Tennessee
Edward Lebovitz, Pittsburgh, Pennsylvania
Arthur M. Master, New York City
Robert L. Mayock, Philadelphia, Pennsylvania
Donald R. McKay, Buffalo, New York
Frank A. Merlino, Providence, Rhode Island
J. Arthur Myers, Minneapolis, Minnesota
Dan C. Ogle (Maj. Gen.), Washington, D. C.
Arthur M. Olsen, Rochester, Minnesota
J. Winthrop Peabody Sr., Washington, D. C.
Charles K. Petter, Waukegan, Illinois
Joseph C. Placak, Abingdon, Virginia
Coleman B. Rabin, New York City
Alfred A. Richman, New York City
Arnold B. Rilance, New Haven, Connecticut
Peter A. Theodos, Philadelphia, Pennsylvania
Howard S. Van Ordstrand, Cleveland, Ohio
David H. Waterman, Knoxville, Tennessee
Irving Willner, Newark, New Jersey
Roy A. Wolford, Washington, D. C.
Murray Kornfeld, Executive Director, Chicago, Illinois
Harriet L. Kruse, Executive Assistant, Chicago, Illinois
Margaret Rogers, Executive Assistant, Chicago, Illinois

JOINT MEETING, BOARD OF GOVERNORS AND BOARD OF REGENTS

A joint luncheon meeting of the Board of Governors and Board of Regents of the College was held at the Warwick Hotel, Philadelphia, on Tuesday, December 3, 1957. Dr. David H. Waterman, chairman of the Board of Governors, presided at the meeting. Dr. Robert V. Cohen, chairman of the program committee for the Interim Session of the College, was introduced and the members of the Board of Governors and Regents expressed their appreciation to him and his committee for the outstanding scientific program which had been presented on the previous day. Drs. Katharine R. Boucot and Robert L. Mayock, President and Secretary of the Pennsylvania Chapter of the College, were introduced and received the congratulations of the assembled officials for the splendid hospitality extended by the members of the Chapter.

The following reports were presented:

Report of the Committee on Scientific Program

24th Annual Meeting, San Francisco, June 18-22, 1958

Samuel Bellet, Chairman
Section on Cardiovascular Diseases

Peter A. Theodos, Chairman
Section on Pulmonary Diseases

Drs. Bellet and Theodos reported that plans for the scientific program to be presented in San Francisco are well under way and every effort will be made to complete the program promptly in order that it may be published in an early issue of *Diseases of the Chest*.

Report of the Committee on Membership

Chevalier L. Jackson, Chairman

Between March 1 and September 1, 1957, 333 applications from all parts of the world were received and presented to the Board of Regents. Of these applications, 162 were for Fellowship, 53 for Associate Fellowship, 82 for Associate Membership and 36 for advancement to Fellowship. Of this group, 166 applications were filed by physicians in the United States and Canada and 167 by physicians in other countries. It should be noted that the 167 applications from countries other than the United States and Canada include some 60 applications which were filed after the September 1 deadline. Twelve of the physicians in the United States and Canada who applied for Fellowship have been reclassified as Associate Fellows. These applications were handled promptly in order to be able to include the listings in the 1958 edition of the Directory of the College.

With the addition of 294 new members in all parts of the world, the total membership of the College is now 6166. As of November 15th, there were 45 applications pending presentation to the Board of Regents at the Annual Meeting. Others will, of course, be received between now and March 1, 1958.

Report of the Editorial Board

J. Arthur Myers, Editor-in-Chief

The Editorial Board is pleased to report on the progress of *Diseases of the Chest* for the year 1957. During the year, approximately 80 per cent of the space in the journal was devoted to the publication of scientific articles and College news. We published 154 scientific articles in 1957, as compared to 141 in 1956.

The current circulation of the journal is 8,100 copies monthly which reach 88 countries and territories throughout the world. Effective January, 1958, with the addition of new members, the circulation will reach 8,400 copies monthly which will be the largest circulation the journal has enjoyed.

Report of the Board of Examiners

Coleman B. Rabin

Twenty-one candidates for Fellowship in the College are being examined in Philadelphia today. Of these, 4 are retaking the examination at the request of the Board of Examiners.

We have 72 other members to be examined and it is expected that the majority of these will take the examinations in San Francisco next June. They will be classified as Associate Fellows until they have successfully completed the examinations.

Report of the Council on Postgraduate Medical Education
J. Winthrop Peabody Sr., Chairman

Three postgraduate courses on diseases of the chest were presented by the College this fall: The 12th Annual Chicago Course was held at the Hotel Knickerbocker, October 21-25, in which 53 physicians were registered; the 10th Annual New York City Postgraduate Course, November 12-16, was presented at the Park Sheraton Hotel and registered 119 physicians; and the 3rd Annual California Course was held at the Ambassador Hotel in Los Angeles, December 9-13, with a registration of 104. Our Council is pleased to report that the 11th Annual Postgraduate Course on Diseases of the Chest will be presented in Philadelphia, March 3-7, at the Warwick Hotel, and the 4th Southern Postgraduate Course is scheduled to be held at the Grady Memorial Hospital, Atlanta, Georgia, in cooperation with Emory University, during the week March 10-14, 1958.

During the period from 1946 through 1957 the College has presented fifty postgraduate courses on diseases of the chest in the United States with the registration totaling 3,533. This is in addition to the many fine postgraduate courses presented under the auspices of College chapters in other countries. It is the aim of your Council on Postgraduate Medical Education to continue this teaching program in order that many more physicians may avail themselves of the opportunity to keep abreast of the advances made in the diagnosis and treatment of heart and lung conditions.

Report of the Committee on Bronchoesophagology
Arthur M. Olsen, Chairman

Since the annual meeting of the College in June, the Committee on Bronchoesophagology has been increased in size by the addition of 5 new members. The full membership of the committee now totals 15.

During the past year the major project of the Committee on Bronchoesophagology has been a study on bronchography. This study was carried out by means of personal communication with 57 men who make bronchograms. These men were drawn from the specialties of radiology, thoracic surgery and ENT (bronchoesophagology). The report was given as part of the scientific program at the annual meeting of the College in May, 1957 and will be printed soon in *Diseases of the Chest*.

At its recent meetings the committee has considered and discussed at length a variety of subjects within the field of bronchoesophagology. These include (1) problems in the training of bronchoesophagologists (editorial *Diseases of the Chest*, December, 1955), (2) bronchography, (3) complications of esophagoscopy and bronchoscopy and their prevention, (4) foreign bodies—who will remove them?, (5) anesthesia for peroral endoscopy, discussion of an analysis of various agents, (6) endoscopic photography in the teaching of bronchoesophagology, (7) esophageal motility studies, (8) study of bronchial anatomy and bronchial nomenclature, (9) cinematography of the esophagus.

As a project for 1958 we are planning to prepare an editorial which will call attention to the value of endoscopic photography in the teaching of bronchoesophagology. Although we do not expect to make bronchoesophagologists out of medical students, we do feel that they should be thoroughly acquainted with the field so that many of them can take up the specialty at a postgraduate level.

Report of the Committee on Cardiovascular Disease
Arthur M. Master, Chairman

The Sections on Cardiovascular Disease of the American College of Chest Physicians can look forward to making significant contributions to progress and education in their respective fields. The possibilities are manifold. The chief reason for my confidence is the fact that the country's best cardiologists are now enrolled and actively participating in our organization.

There are now seven sections in Cardiovascular Disease:

Section on Clinical Cardiovascular Disease
Eliot Corday, Beverly Hills, California, Chairman

Section on Angiocardiography
Israel Steinberg, New York, N. Y., Chairman

Section on Cardiovascular Surgery
Charles P. Bailey, Philadelphia, Pennsylvania, Chairman

Section on Rehabilitation
H. Easton McMahon, New York, N. Y., Chairman

Section on Electrocardiography
Irving Mack, Chicago, Illinois, Chairman

Section on Cardiovascular Physiology
John J. Sampson, San Francisco, California, Chairman

Section on Pediatric Cardiology
Benjamin M. Gasul, Chicago, Illinois, Chairman

I respectfully suggest that there is a need for two more sections to be constituted; one on "Hypertension" and another on "Roentgenography of the Heart." The latter group could probably operate within the framework of the already active Section on Angiocardiography or vice versa.

It is important that the programs of all these sections be coordinated, and this can best be done at a Chairmen's meeting held at least twice yearly. In the past, this has not worked out as well as it might. It would probably be most convenient for such conferences to be held at the annual meeting place and in Chicago.

To my mind, a most valuable project for us to concentrate on would be, in broad terms, "Recent Advances in Cardiovascular Diseases." This would include progress in diagnostic techniques, therapy, changing patterns of disease, etc., all of which would be culled from the many contributions made at our own meetings.

We should plan to have certain topics pre-selected by the program committee, covered thoroughly from every aspect at each of our annual and interim meetings. This need not interfere with the plans of any contributor to publish his own work independently, if he so wished.

The chairmen of the sections on cardiovascular disease, the program committees who supervise the agenda of the Seminars, Scientific Lectures, Luncheon Panels and Fireside Conferences at the annual meetings, would delineate the scope of "recent advances in cardiovascular diseases, medical and surgical," always correlating with pulmonary disease, whenever possible. Symposia on pertinent, provocative, up-to-the-minute problems of cardiovascular disease, both from the medical and surgical viewpoint, should be planned. These should deal, not only with current progress but indicate the direction of future research.

Thus, a *Seminar* on a topic such as *angina pectoris due to coronary disease* would include a physician to review the problem of chest pain, and another physician to relate the natural history of angina pectoris. After all, there must be control data in order for the surgeons to evaluate old and new operative procedures which they, of course, would present. There is now extant a fairly good natural history of angina pectoris, e.g., White and Bland; Weiss and Weiss; Master, Jaffe and Dack; insurance material and others. The surgeons would submit the latest in their procedures for the alleviation or cure of coronary disease.

There are many similar timely topics with their dramatic and kaleidoscopic advances from which to choose. To mention but a few, extracorporeal circulation for open heart surgery; the surgical correction of aortic stenosis; or aortic insufficiency; left heart catheterization; angiocardiography and roentgenography in the diagnosis of congenital and acquired heart disease; serum enzyme determinations in myocardial necrosis, all lend themselves for review both by internists and surgeons. Wherever indicated, the natural course of the disease would first be described, e.g., in aortic stenosis and also in aortic insufficiency.

The SGO-T determination is replacing the sedimentation rate test. In fact, in my opinion, the latter is useless in coronary artery disease but the transaminase reading is becoming invaluable for determination of myocardial injury. In acute

coronary insufficiency, it would be particularly useful. Again, Isuprel and adrenal corticosteroids in heart block; new antihypertensive therapy, normal blood pressure from birth to old age; are all of interest and of paramount importance to the up-to-date internist. In summary, then, the "headlines" in medicine would be surveyed at our annual and interim meetings.

The *Scientific Sessions* program would be similarly planned with the same general topics. Not only would the speakers submit papers in advance but the discussors, too. If they wish, the latter could alter their 5 minute paper after the meeting, if a change is desired.

The *Round Table Luncheon Meetings* would be programmed, again, with at least a few definitely chosen topics in mind. The 4 or 5 speakers would prepare 10 minute papers in advance. Stenographic records could be made and later edited, of the questions and answers following the 10 minute talks, or the moderator or an associate moderator could jot these down. If the moderator insists, as he should, on brief, succinct, interrogation and the same type of reply, much territory will be covered. The questioner should not be permitted to make a speech, nor to ask a "discuss" type of question. Thus, the formal written talks, and the questions and answers which follow, would constitute a good review and help round out similar contributions in the seminars and in the scientific sessions.

Fireside Conferences can also, in part, be designed to survey the major topics chosen for the particular annual or interim session or sessions. One or two volunteers would be given pad and pencil and the discussion leader could always briefly repeat the question to him and briefly summarize each answer. I find I do this naturally at most such conferences.

Our *Council on Undergraduate Medical Education* might take advantage of much of the material and organize a teaching project on the undergraduate level, derived from these planned topics.

In conclusion, then, without belaboring these ideas any further, I am confident that much can be done by the American College of Chest Physicians through the Sections on Cardiovascular Disease. With planned initiative and imagination on our part, medicine will look to the American College of Chest Physicians for leadership in teaching and research.

Report of the Committee on Pulmonary Diseases in Children

Roy F. Goddard, Chairman

The Committee on Pulmonary Diseases in Children was created at the Interim Session of the College held in Seattle in December, 1956 with a membership of five. Informal meetings of the committee were held in Chicago in January and October, and the first annual meeting was held in New York City in June of 1957, during the 23rd annual meeting of the College. The committee has now been enlarged to 26 members. A good number of members were present for our committee meeting held today.

Among the projects of our committee for the coming year are the following: 1) Pulmonary function in the toddler age group (1-6 years); 2) Continuing studies on mechanics of breathing in the newborn and pulmonary function studies in older children; 3) Benefit of certain surgical procedures in improving pulmonary function in children with poliomyelitis and other respiratory disorders. The committee is also cooperating with the Committee on Scientific Program in planning for the discussion of pulmonary diseases in children at the next annual meeting of the College.

The committee has recommended the reappointment of Dr. Milton Levine, New York City, as representative to the 1960 White House Conference on Children and Youth.

We believe that the past six months has seen considerable new interest stimulated in pulmonary problems in children and the beginning of an active group to carry out the functions and objectives of the committee outlined in our first report to the Board of Regents last June.

Report on College Books

Clinical Cardiopulmonary Physiology

Burgess L. Gordon, Chairman, Editorial Committee

It is gratifying to report that over 2,000 copies of the book have been sold during the past year, since its publication early in 1957. We have been advised by Grune & Stratton, Inc., the publishers, that they are negotiating with foreign publishers relative to translation and publication of the book in other countries.

Roentgenology of the Chest

Coleman B. Rabin, Chairman, Editorial Committee

We have been informed by the publisher, Charles C Thomas, that our new book will be available in February. It is anticipated that the book will have between 500 and 600 pages; the book will have many excellent illustrations and the format we believe is most attractive and the text easily read. This book, we are sure, will be a credit to the growing list of books published by the College and we anticipate that it will be well received.

SEMI-ANNUAL MEETING, BOARD OF REGENTS

The Board of Regents of the College held its semi-annual meeting on Tuesday afternoon, December 3, at the Warwick Hotel, Philadelphia. Dr. John F. Briggs, chairman, presided.

Dr. Petter, Treasurer of the College, presented the financial report and 1958 budget which were unanimously accepted. The report of the Committee on Insurance was referred to committee for further study.

Dr. Childerhose reported for the Committee on Medical Practice, on which he serves as vice-chairman. The committee will convene in San Francisco to give further study to their program.

Colonel James A. Wier, chairman of the Committee on Chemotherapy and Antibiotics submitted a report to the effect that they plan to complete the report on the chemotherapy of non-tuberculous diseases of the chest and have it ready for publication shortly. The report was revised at the annual meeting of the committee in New York and a new draft has been completed. At present it is being submitted to the committee members for comments and approval.

The following report received from Dr. Alexander Libow, chairman of the Committee on Non-Surgical and Drug Therapy, stated: It has been the custom of this committee to review current therapy in pulmonary tuberculosis every five years. This has been accomplished by presenting ten standard cases to one hundred participating chest physicians from all parts of the country. The same ten cases are to be presented, with changes in therapy, and the comments of the participating physicians are compared with each other and with the previous five year report. It is almost five years since the last report was published and the committee plans to present this work once more. Several other projects under consideration by the committee are "Use of Bed Rest in the Treatment of Tuberculosis," "Treatment of Tuberculosis in Out-Patient Clinics," and the "Home Treatment of Tuberculosis." Other projects will undoubtedly be suggested by members of the committee and they will be explored.

Dr. Robert J. Anderson, chairman of the Council on Public Health, submitted the following report: The Council on Public Health proposed to prepare timely articles on respiratory disease subjects to the membership through *Diseases of the Chest*. Influenza caused by Asian A virus was the subject of the first article which was presented in the August issue of the College journal. This was one of the first reports to appear in scientific journals regarding this problem. As all of the members well know, the problem is still with us but I believe it is at its peak at this time and we look forward to a falling incidence very soon. Some areas of the country have already experienced the full impact of the epidemic. Several things are noteworthy in this epidemic. It was forecast quite accurately with the exception that the peak was reached slightly earlier than was expected. Advance preparations were initiated by the medical and public health professions which I am sure have blunted the impact of the epidemic. The additional mortality of the epidemic has been small as a consequence. The opportunity for research upon influenza has been seized by the investigators of the Public Health Service,

the Armed Forces, and the universities over the country, so that we shall be better prepared to act when the next influenza epidemic appears on the horizon. The Council on Public Health will try to keep the membership informed and alerted to respiratory disease problems of interest to the membership.

Dr. Alfred Goldman (Los Angeles), chairman of the Committee on Pulmonary Surgery, reported that his group has been concerned with the collection of approximately 1000 cases of mass x-ray survey type malignant neoplastic lesions of the lung (coin lesions). The cure rate of this type of lesion by surgical resection is still unknown. The published reports of a small series of such lesions resected indicate that there is a large increase in the 5 year survival rate compared to the 5 year survival rate of cancer of the lung not discovered in its asymptomatic early stage. By collecting data on a large series of this type of early asymptomatic cancer of the lung surgically resected, a more accurate appraisal of the 5 year survival time can be made. It is anticipated that a complete report of our study may be available by the time of our annual meeting in San Francisco next June.

The following report was submitted by Dr. Arthur W. Dahlstrom, chairman of the Committee on Indian Affairs, concerning the New Mexico Field Tuberculosis Study: There is little to report on the progress of the study program to date. Influenza has interfered with the tuberculin testing of the group that has this fall completed the therapy. The last of the 20 schools will be tested December 2. The figures are being assembled and the control-placebo code will then be opened and the results tabulated and sent to the university for evaluation. The larger group will have completed their therapy next spring. It is hoped that some definite figures will be available by the time of the next annual meeting in San Francisco.

Dr. Robert B. Stone, chairman of the Committee on Audiovisual Aids, advised the Board that his committee is assembling a new collection of 35 mm lantern slides which may be used for teaching diseases of the chest to undergraduate medical students. It is hoped that the collection will be completed prior to the annual meeting of the College in San Francisco and may be exhibited at that time.

The following resolutions were presented and approved:

WHEREAS, The American College of Chest Physicians is an international organization with more than 6,000 members in 86 countries and territories, and

WHEREAS, The College has organized, since 1950, four successful international congresses on diseases of the chest, and The Fifth International Congress of the College will be held in Tokyo, Japan, September 7-11, 1958, and

THEREFORE BE IT RESOLVED, That the Board of Regents of the College authorize the establishment of international committees to provide further opportunities for our members throughout the world to contribute to the advancement of the College program, and

WHEREAS, Most of the work of the College is conducted through its councils and committees,

BE IT FURTHER RESOLVED, That these international committees shall meet at the time and place of the international congresses sponsored by the American College of Chest Physicians, and

BE IT FURTHER RESOLVED, That the President of the College be authorized to appoint such committees.

WHEREAS, The Research and Education Foundation for Chest Disease has been reorganized according to a resolution adopted by the Board of Regents of the College at its last annual meeting in New York City, June, 1957, and

WHEREAS, It has taken several months to conduct the reorganization and preparation of literature for the foundation, and

WHEREAS, A great deal of the preliminary work essential to the raising of funds for research has been accomplished, and

WHEREAS, The initial appropriation of $5,000.00 has been utilized for this purpose, and

WHEREAS, It is requested that an additional sum of $5,000 be appropriated for the Foundation by the Council on Research of the College, and

WHEREAS, Mr. Ward Bentley, the Executive Secretary of the Foundation, has expressed an opinion that there is every possibility, given more time, for the Foundation to succeed in its efforts to raise research funds,

THEREFORE BE IT RESOLVED, That the Council on Research of the American College of Chest Physicians advance $5,000.00 of its funds to the Research and Education Foundation for Chest Disease for the purpose of defraying the cost of its operation during the year 1958, and

BE IT FURTHER RESOLVED, That the Council on Research be authorized to enter into negotiations with Mr. Ward Bentley for a retainer fee for this period of time.

Mr. Kornfeld reported on his recent trip to the Orient and acquainted the members of the Board of Regents with the arrangements that have been completed for the Fifth International Congress on Diseases of the Chest to be held in Tokyo, September 7-11, 1958. The first article dealing with the Congress in Tokyo and the post-congress tour of Japan appears in this issue of the journal. Additional articles concerning the congress and the post-congress tour will be published in future issues.

COLLEGE ANNOUNCES NEW CARDIOVASCULAR SECTION

We wish to announce, effective with this issue, the Section on Cardiovascular Diseases which will appear as a regular feature in *Diseases of the Chest*. We trust that College members and subscribers to our journal will be pleased with this new section and the Editorial Board invites comments and suggestions.

It is the objective of the Editorial Board to keep the material published in *Diseases of the Chest* current and of interest to our readers and we trust that the addition of this new section will add another milestone in the progress being made in the specialty of chest diseases.

College Chapter News

NEW ENGLAND STATES CHAPTER

The New England States Chapter will present the following scientific program at its meeting to be held on January 11, 1958, at the Dowling Amphitheater of the Boston City Hospital:

9:00 a.m. Registration

9:30 a.m. "Antimicrobial and Steroid Therapy in Diseases of the Chest: Resident Organisms—Staphylococcus Infection-Influenza, 1957" (panel)

Moderator: Maxwell Finland, Boston

Panel: Edward H. Kass, Calvin N. Kunian, Christopher Martin, and Louis Weinstein, Boston

11:00 a.m. "Stump the Experts" (x-ray panel)

Moderator: Max Ritvo, Boston

Panel: S. Clive Cohen, James B. Dealy, Jr., Richard H. Overholt, and Stanley M. Wyman, Boston

12:30 p.m. Luncheon and visit to the research laboratories of the Boston City Hospital

2:00 p.m. "Airspace Disorders" (panel)

Moderator: John W. Strieder, Boston

Panel: Theodore Badger, Edward A. Gaensler, Joseph P. Lynch, and Lamar Soutter, Boston

"Chronic Dyspneic Diseases—Physiology and Treatment" (panel)

Moderator: Maurice S. Segal, Boston

Panel: Ernst O. Attinger, Boston; Alvan L. Barach, New York City; Jeremiah E. Greene, Boston; and Edwin R. Levine, Chicago

5:30 p.m. Cocktail party and dinner, Harvard Club

NEW CHAPTER OFFICERS

NEW ENGLAND STATES CHAPTER

President:	Maurice S. Segal, Boston, Massachusetts
1st Vice-President:	Joseph N. Corsello, Providence, Rhode Island
2nd Vice-President:	Francis D. T. Bowen, Hartford, Connecticut
Secretary-Treasurer:	S. Clive Cohen, Boston, Massachusetts (re-elected)

SOUTHERN CHAPTER

President:	Joseph S. Cruise, Atlanta, Georgia
1st Vice-President:	Daniel E. Jenkins, Houston, Texas
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PUERTO RICO CHAPTER

President:	Jose L. Porrata, Hato Rey
Vice-President:	Jose Amadeo, Aibonito
Secretary-Treasurer:	Hilarion Sanchez, Rio Piedras

NEWS NOTES

Dr. Joseph B. Stocklen, Cleveland, Ohio was awarded the Dearholt Medal, the highest award given by the Mississippi Valley Conference on Tuberculosis. The medal is awarded to an individual for outstanding contributions to tuberculosis control.

Dr. Jay Arthur Myers, Minneapolis, Minnesota, Editor-in-Chief of *Diseases of the Chest,* received the William A. Howe Honor Award from the American School Health Association at the annual banquet of the association held in Cleveland, Ohio, November 13.

Dr. William H. McCain, formerly internist at St. John's Sanatorium and Crippled Children's Hospital in Springfield, Illinois, has been appointed Medical Director of the Hillcrest Sanatorium, Quincy, Illinois.

Prof. Manoel de Abreu, Rio de Janeiro, Brazil, Regent of the College, was honored on his birthday, January 4, by the Paulista Association of Chest Diseases in Sao Paulo, his birthplace. This date has been officially set aside as the "Day of Abreugraphia" in homage to Prof. de Abreu whose research and eventual development of the 35mm film marked the beginning of mass chest x-ray as we know it today. The association plans to celebrate this date annually and will present a scientific program dealing with the fight against tuberculosis.

The following Fellows of the College were recently appointed by William G. Stratton, Governor of the State of Illinois, to the advisory committee on tuberculosis, which serves as an advisory body to the tuberculosis control service of the state: **William E. Adams,** Chicago; **Eugene J. Des Autels,** Hines; **Leonard Krasner,** Downey; **Hiram T. Langston,** Chicago; **William Lees,** Chicago; **Dan Morse,** Peoria; **Julius B. Novak,** Chicago; **Edward A. Piszczek,** Chicago; and **George C. Turner,** Chicago. **Drs. Kenneth G. Bulley,** Aurora; **Clifton Hall,** Springfield; and **David B. Radner,** Chicago, were re-appointed to the committee.

Dr. Otto L. Bettag, Chicago, Director of Public Welfare for the state and Regent of the College, and **Dr. Ernest Teller,** Chicago, Chief of the Tuberculosis Control Service, serve as ex-officio members. **Dr. Bettag** was also reappointed by Governor Stratton to a second term as member of the Medical Center Commission.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Internist and physiologist, eligible for American Board of Internal Medicine examination, Ph.D. (physiology) with 7 years' experience in research in respiration and circulation, trained and experienced in pulmonary function testing; experience as staff member, tuberculosis sanatorium; presently member of faculty of grade A medical school, desires position in which clinical medicine and clinical research can be combined in above fields of interest. Please address inquiries to Box 296B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Associate Member, American College of Chest Physicians, age 40, lung specialist from Paris, former director of chest hospital in Middle East, consultant physician at chest hospital and on faculty of medicine in Southeast Asia, clinical experience, seeks position in chest hospital. Please address inquiries to Box 956, Stanford University, Stanford, California.

POSITIONS AVAILABLE

Full-time staff physician wanted for the Idaho State Tuberculosis Hospital, Gooding, Idaho. New, fully modern hospital building recently completed, replacing several small antiquated units. Total bed capacity of 85. Salary governed by training and experience. Apply: Medical Director, Idaho State Tuberculosis Hospital, Gooding, Idaho.

Resident physician wanted with chest experience, eligible for New Jersey license. 240-bed general chest disease hospital, with surgical department. Position open February 1, 1958. Maintenance with private apartment available. Communicate with: Medical Director, Passaic County Valley View Hospital, Box 1608, Paterson, New Jersey.

Asthma. Well-known hospital, expanding pediatric and asthma program, seeks internist with special interest in asthma to head service. Such a man would come in on ground floor and help develop complete program involving psychiatric, allergy, and cardio-pulmonary services. Social service, total patient rehabilitation, and research are major elements of program. State salary required. Please address inquiries to Box 294A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Full-time physician wanted for new 440-bed tuberculosis division of large general hospital in the east. Associated with two medical schools for teaching purposes, with opportunity for research. Complete surgical and pathological facilities. Please address inquiries to Box 295A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff physician wanted for 600 bed, modern tuberculosis hospital. Medical license or eligibility required. Hospital located in college town, 30,000. Active outpatient department. Suspected cases admitted for diagnosis. Vacation, sick leave, retirement and social security. Salary $9360 up, depending on qualifications. Apply: Medical Director, Eastern North Carolina Sanatorium, Wilson, North Carolina.

Two physicians wanted for approved residency in tuberculosis and pulmonary diseases. 200-bed hospital, integral part of medical school and the primary general teaching hospital. Residency includes 3 months' elective training in related fields such as cardiopulmonary laboratory, research, bacteriology laboratory, infectious diseases. Salary $225 month minimum. Please address inquiries to Medical Director, Woodlawn Hospital, 3819 Maple Avenue, Dallas, Texas.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSES

11th Annual Postgraduate Course on Diseases of the Chest
Warwick Hotel, Philadelphia, March 3-7, 1958

4th Southern Postgraduate Course on Diseases of the Chest
Grady Memorial Hospital, Atlanta, Georgia, March 10-15, 1958

CHAPTER MEETING

Clinical Meeting, New York State Chapter, New York City
February 20-21, 1958

Important!

San Francisco Hotel Reservations

24th ANNUAL MEETING, AMERICAN COLLEGE OF CHEST PHYSICIANS

Fairmont Hotel, San Francisco, June 18-22, 1958

Members planning to attend *only* the College meeting in San Francisco must complete the coupon on this page and mail it to the Convention Bureau together with a deposit in the amount of $10.00 for each room requested.

Members planning to attend the College meeting and *all or a portion* of the meeting of the American Medical Association, June 23-27, must attach a room reservation form clipped from an issue of the Journal of the A.M.A. to the form appearing below and mail *both coupons,* together with a deposit in the amount of $10.00 per room, directly to the San Francisco Convention and Visitors Bureau. We have been informed that the A.M.A. reservation form will appear in the January 4, 1958 issue of the J.A.M.A.

Members of the College are urged to submit their reservation forms to the San Francisco Convention and Visitors Bureau at the earliest possible date in order to be assured of accommodations at one of the hotels easily accessible to the Fairmont Hotel.

DON'T DELAY—DO IT TODAY

San Francisco Convention and Visitors Bureau
300 Civic Auditorium
San Francisco 2, California

I am planning to attend the 24th ANNUAL MEETING, AMERICAN COLLEGE OF CHEST PHYSICIANS, FAIRMONT HOTEL, SAN FRANCISCO, JUNE 18-22, 1958. Please reserve the following accommodations for which I am enclosing a deposit in the amount of $10.00.

Name .....

Accompanied by .....

Address .....

City and State .....

Single Room ..... Twin Bedroom ..... Suite .....

Arrival Date ..... Departure Date .....

HOTEL—Please indicate by number your choice of hotels

Fairmont Hotel	Sir Francis Drake Hotel .....
Mark Hopkins Hotel	Canterbury Hotel .....
Huntington Hotel	Colonial Hotel .....
St. Francis Hotel	Motel .....

✶✶ PLAN A TRIP TO TOKYO

For The

FIFTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Sponsored by the Council on International Affairs
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Presented under the Patronage of the
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TOKYO, JAPAN **SEPTEMBER 7-11, 1958**

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Upon completion of arrangements for the tours, a printed brochure containing all pertinent information will be made available by Cartan Travel Bureau, Inc., Chicago, official travel agency for the Congress.

For further information please write to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois

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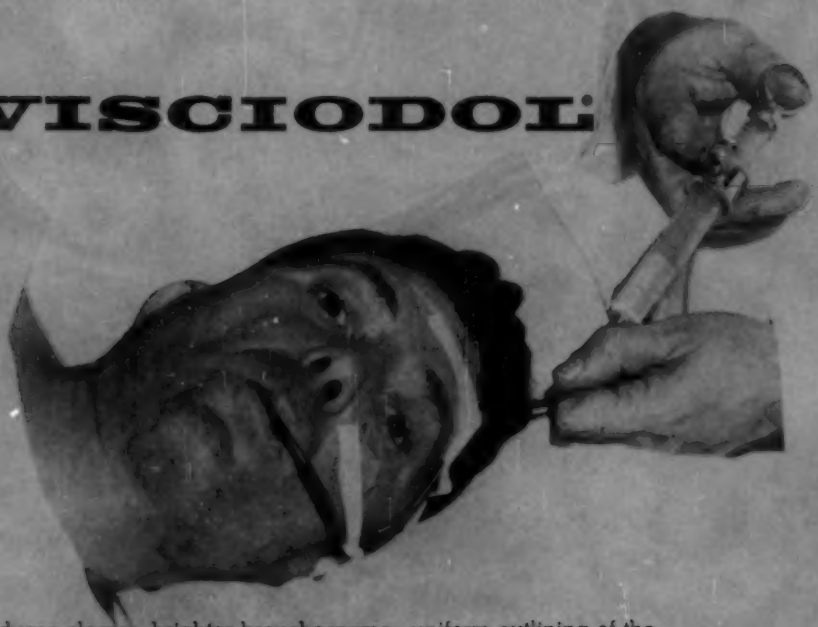

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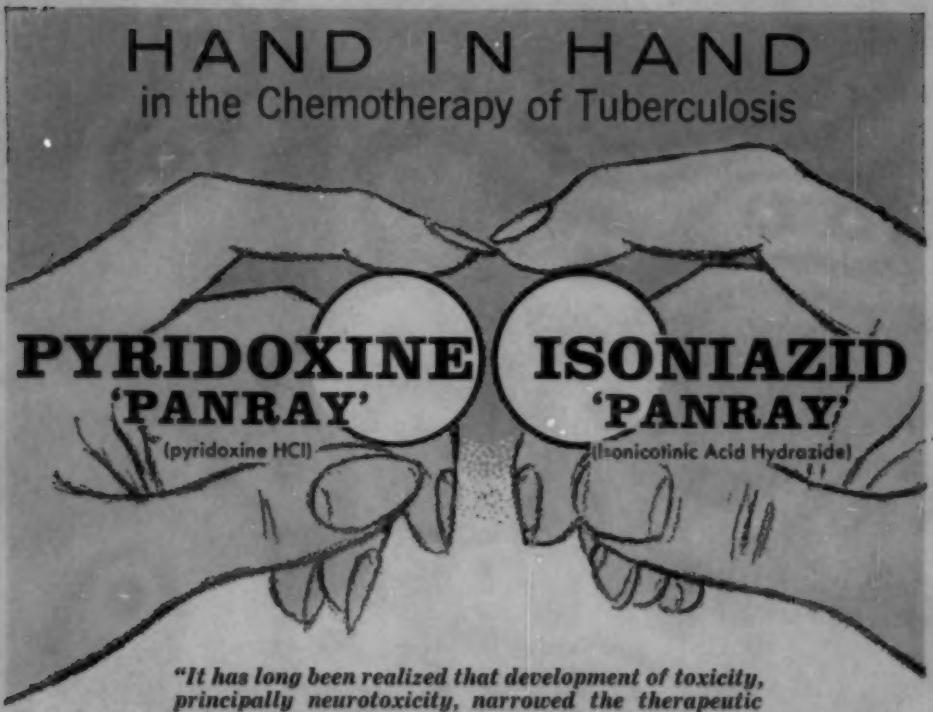

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[1]See View Bulletin 16:62 July '56 Tchertkoff, et al. JAMA 156:1549 (Dec. 25) 1954 Biehl & Viltner Am. Rev. TBc 70:266 Aug. '54 Hughes, et al. N. Eng. J. of Med. 255 #3 118-122, 1956 Carlson, et al.